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(54) Title: PIPERAYINE DERIVATIVES FOR TREATMENT OF BACTERIAL INFECTIONS

(57) Abstract: Piperazine derivatives and pharmaceutically acceptable derivatives thereof useful in methods of treatment of bacterial infections in mammals, particularly in man(represented by formula (I).

PIPERAZINE DERIVATIVES FOR TREATMENT OF BACTERIAL INFECTIONS

This invention relates to novel compounds, compositions containing them and their use as antibacterials.

WO99/37635, WO00/21948 and WO00/21952 disclose piperidine derivatives having antibacterial activity.

EP0579263, EP0742207, JP2169569 and EP0296560, generically disclose piperazine compounds as acetylcholinesterase inhibitors and sigma receptor antagonists

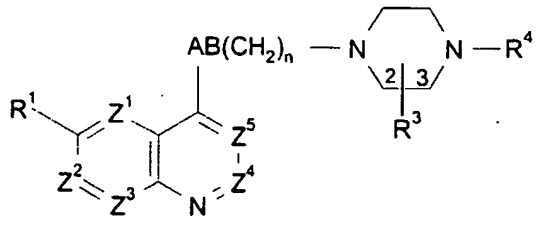
WO92/17475, WO98/02438, WO97/03069 and WO96/39145 disclose certain bicyclic heteroaromatic compounds having cholinesterase inhibitor, protein tyrosine kinase inhibitor, cell proliferation inhibitor and human epidermal growth factor receptor type 2 inhibitor activity.

JP7179407 discloses bicyclic heteroaromatic compounds having GPIIb/IIIa inhibitory activity

WO97/17973 discloses piperazine derivatives having hemoregulatory activities.

WO99/05096 discloses naphthamidine compounds having urokinase inhibitory activity.

This invention provides a compound of formula (I) or a pharmaceutically acceptable derivative thereof:



(I)

wherein:

one of Z^1, Z^2, Z^3, Z^4 and Z^5 is N, one is CR^{1a} and the remainder are CH, or one of Z^1, Z^2, Z^3, Z^4 and Z^5 is CR^{1a} and the remainder are CH;

R^1 and R^{1a} are independently selected from hydrogen; hydroxy; (C_{1-6}) alkoxy optionally substituted by (C_{1-6})alkoxy, amino, piperidyl, guanidino or amidino any of which is optionally N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{1-6})alkoxy-substituted (C_{1-}

$_{6}$)alkyl; halogen; (C_{1-6})alkyl; (C_{1-6})alkylthio; trifluromethyl; nitro; azido; acyl; acyloxy; acylthio; (C_{1-6})alkylsulphonyl; (C_{1-6})alkylsulphoxide; arylsulphonyl; arylsulphoxide or an amino, piperidyl, guanidino or amidino group optionally N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups,

provided that when none of Z^1, Z^2, Z^3, Z^4 and Z^5 is N, then R^1 is not hydrogen;

R^3 is hydrogen; or

R^3 is in the 2- or 3-position and is:

carboxy; (C_{1-6})alkoxycarbonyl; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, trifluoromethylsulphonyl, (C_{2-6})alkenylsulphonyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl or (C_{2-6})alkenyl; cyano; tetrazolyl; 2-oxo-oxazolidinyl optionally substituted by R^{10}; 3-hydroxy-3-cyclobutene-1,2-dione-4-yl; 2,4-thiazolidinedione-5-yl; tetrazol-5-ylaminocarbonyl; 1,2,4-triazol-5-yl optionally substituted by R^{10}; or 5-oxo-1,2,4-oxadiazol-3-yl; or

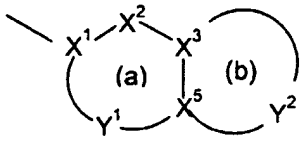
(C_{1-4})alkyl or ethenyl optionally substituted with any of the groups listed above for R^3 and/or 0 to 2 groups R^{12} independently selected from:

halogen; (C_{1-6})alkylthio; trifluoromethyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; (C_{2-6})alkenylcarbonyl; hydroxy optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylcarbonyl or (C_{2-6})alkenylcarbonyl; amino optionally mono- or disubstituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, (C_{2-6})alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl or (C_{2-6})alkenyl; oxo; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or (C_{1-6})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;

in addition when R^3 is disubstituted with a hydroxy or amino containing substituent and a carboxy containing substituent these may optionally together form a cyclic ester or amide linkage, respectively;

R^{10} is selected from (C_{1-4})alkyl; (C_{2-4})alkenyl and aryl any of which may be optionally substituted by a group R^{12} as defined above; carboxy; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, trifluoromethylsulphonyl, (C_{2-6})alkenylsulphonyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl;

R^4 is a group –U-V-R^5 where R^5 is an optionally substituted bicyclic carbocyclic or heterocyclic ring system (A):



(A)

containing up to four heteroatoms in each ring in which

at least one of rings (a) and (b) is aromatic;

X^1 is C or N when part of an aromatic ring or CR^{14} or N when part of a non aromatic ring;

X^2 is N, NR^{13}, O, $S(O)_x$, CO or CR^{14} when part of an aromatic or non-aromatic ring or may in addition be $CR^{14}R^{15}$ when part of a non aromatic ring;

X^3 and X^5 are independently N or C;

Y^1 is a 0 to 4 atom linker group each atom of which is independently selected from N, NR^{13}, O, $S(O)_x$, CO and CR^{14} when part of an aromatic or non-aromatic ring or may additionally be $CR^{14}R^{15}$ when part of a non aromatic ring,

Y^2 is a 2 to 6 atom linker group, each atom of Y^2 being independently selected from N, NR^{13}, O, $S(O)_x$, CO and CR^{14} when part of an aromatic or non-aromatic ring or may additionally be $CR^{14}R^{15}$ when part of a non aromatic ring;

each of R^{14} and R^{15} is independently selected from: H; (C_{1-4})alkylthio; halo; carboxy(C_{1-4})alkyl; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl; (C_{1-4})alkoxycarbonyl; formyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; (C_{1-4})alkylcarbonyloxy; (C_{1-4})alkoxycarbonyl(C_{1-4})alkyl; hydroxy; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group

is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl; aryl; aryl(C_{1-4})alkyl; aryl(C_{1-4})alkoxy;

each R^{13} is independently H; trifluoromethyl; (C_{1-4})alkyl optionally substituted by hydroxy, (C_{1-6})alkoxy, (C_{1-6})alkylthio, halo or trifluoromethyl; (C_{2-4})alkenyl; aryl; aryl (C_{1-4})alkyl; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; formyl; (C_{1-6})alkylsulphonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl, (C_{2-4})alkenylcarbonyl, (C_{1-4})alkyl or (C_{2-4})alkenyl and optionally further substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl;

U is selected from CO, SO_2 and CH_2 and V is $CR^{17}R^{18}$ or U is CH_2 and V is CO or SO_2;

R^{17} and R^{18} are independently selected from hydrogen, hydroxy optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylcarbonyl or (C_{2-6})alkenylcarbonyl; and amino optionally mono- or disubstituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, (C_{2-6})alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;

n is 0 and AB is $NR^{11}CO$, $CO\text{-}CR^8R^9$, $CR^6R^7\text{-}CO$, $NHR^{11}SO_2$, $CR^6R^7\text{-}SO_2$ or $CR^6R^7\text{-}CR^8R^9$, provided that R^8 and R^9 are not optionally substituted hydroxy or amino and R^6 and R^8 do not represent a bond:
or n is 1 and AB is $NR^{11}CO$, $CO\text{-}CR^8R^9$, $CR^6R^7\text{-}CO$, $NR^{11}SO_2$, $CONR^{11}$, $CR^6R^7\text{-}CR^8R^9$, $O\text{-}CR^8R^9$ or $NR^{11}\text{-}CR^8R^9$;

and wherein:
each of R^6, R^7, R^8 and R^9 is independently selected from: H; (C_{1-6})alkoxy; (C_{1-6})alkylthio; halo; trifluoromethyl; azido; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; (C_{2-6})alkenylcarbonyl; hydroxy, amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or (C_{1-6})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;

or R^6 and R^8 together represent a bond and R^7 and R^9 are as above defined;

and each R^{11} is independently H; trifluoromethyl; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl or (C_{2-6})alkenyl and optionally further substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;

or where one of R^3 and R^6, R^7, R^8 or R^9 contains a carboxy group and the other contains a hydroxy or amino group they may together form a cyclic ester or amide linkage.

The invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for use in the treatment of bacterial infections in mammals.

The invention also provides a pharmaceutical composition for use in the treatment of bacterial infections in mammals comprising a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

The invention further provides a method of treatment of bacterial infections in mammals, particularly in man, which method comprises the administration toa mammal in need of such treatment of an effective amount of a a compound of formula (I), or a pharmaceutically acceptable derivative thereof.

In one aspect, when (a) and (b) are both aromatic, -U-V- is not $-CH_2-CO-$ or $-(CH_2)_2-$. In another aspect when -U-V- is $-CH_2-CO-$ or $-(CH_2)_2-$, R^5 is not indolyl, quinolinyl, 1,3-dihydro-2-oxo-benzimidazolyl or benzothienyl.

In another aspect one of U and V are selected from CO, SO_2 and CH_2 and the other is CH_2.

Preferably Z^5 is CH or N, Z^3 is CH or CF and Z^1, Z^2 and Z^4 are each CH, or Z^1 is N, Z^3 is CH or CF and Z^2, Z^4 and Z^5 are each CH

When R^1 or R^{1a} is substituted alkoxy it is preferably (C_{2-6})alkoxy substitituted by optionally N-substituted amino, guanidino or amidino, or (C_{1-6})alkoxy substituted by piperidyl. Suitable examples of R^1 alkoxy include methoxy, n-propyloxy, i-butyloxy, aminoethyloxy, aminopropyloxy, aminobutyloxy, aminopentyloxy, guanidinopropyloxy, piperidin-4-ylmethyloxy, phthalimido pentyloxy or 2-aminocarbonylprop-2-oxy.

Preferably R^1 is methoxy, amino(C_{3-5})alkyloxy, guanidino(C_{3-5})alkyloxy, piperidyl(C_{3-5})alkyloxy, nitro or fluoro; more preferably methoxy, amino(C_{3-5})alkyloxy or guanidino(C_{3-5})alkyloxy. Preferably R^{1a} is H or F. Most preferably R^1 is methoxy and R^{1a} is H or when Z^3 is CR^{1a} it may be C-F.

When Z^5 is CR^{1a}, R^{1a} is preferably hydrogen, cyano, hydroxymethyl or carboxy, most preferably hydrogen.

Preferably n is 0.

Preferred examples of R^3 include hydrogen; (C_{1-4}) alkyl; ethenyl; optionally substituted 1-hydroxy-(C_{1-4}) alkyl; optionally substituted aminocarbonyl; carboxy(C_{1-4})alkyl; optionally substituted aminocarbonyl(C_{1-4})alkyl; cyano(C_{1-4})alkyl; optionally substituted 2-oxo-oxazolidinyl and optionally substituted 2-oxo-oxazolidinyl(C_{1-4}alkyl). More preferred R^3 groups are hydrogen; $CONH_2$; 1-hydroxyalkyl e.g. CH_2OH, $CH(OH)CH_2CN$; CH_2CO_2H; CH_2CONH_2; -$CONHCH_2CONH_2$; 1,2-dihydroxyalkyl e.g. $CH(OH)CH_2OH$; CH_2CN; 2-oxo-oxazolidin-5-yl and 2-oxo-oxazolidin-5-yl(C_{1-4}alkyl). Most preferably R^3 is hydrogen.

When R^3 and R^6, R^7, R^8 or R^9 together form a cyclic ester or amide linkage, it is preferred that the resulting ring is 5-7 membered. It is further preferred that the group A or B which does not form the ester or amide linkage is CH_2.

When A is CH(OH) the R-stereochemistry is preferred.

Preferably A is NH, NCH_3, CH_2, CHOH, $CH(NH_2)$, C(Me)(OH) or CH(Me).

Preferably B is CH_2 or CO.

Preferably n=0.

Most preferably:

n is 0 and either A is CHOH and B is CH_2 or A is NH and B is CO.

Preferably R^{11} is hydrogen or (C_{1-4})alkyl e.g. methyl, more preferably hydrogen.

Examples of –U-V- include $-(CH_2)_2-$, $-CH_2CH(OH)$ and $-CH_2CO-$. The group –U-V- is preferably $-(CH_2)_2-$.

Preferably R^5 is an aromatic heterocyclic ring (A) having 8-11 ring atoms including 2-4 heteroatoms of which at least one is N or NR^{13}.

Alternatively and preferably the heterocyclic ring (A) has ring (a) aromatic and ring (b) non-aromatic and Y^2 has 3-5 atoms including NR^{13}, O or S bonded to X^5 and NHCO bonded via N to X^3, or O or NH bonded to X^3. Examples of rings (A) include optionally substituted:

<u>(a) and (b) aromatic</u>

1H-pyrrolo[2,3-b]-pyridin-2-yl, 1H-pyrrolo[3,2-b]-pyridin-2-yl, 3H-imidazo[4,5-b]-pyrid-2-yl, 3H-quinazolin-4-one-2-yl, benzimidazol-2-yl, benzo[1,2,3]-thiadiazol-5-yl,

benzo[1,2,5]-oxadiazol-5-yl, benzofur-2-yl, benzothiazol-2-yl, benzo[b]thiophen-2-yl, benzoxazol-2-yl, chromen-4-one-3-yl, imidazo[1,2-a]pyridin-2-yl, imidazo-[1,2-a]-pyrimidin-2-yl, indol-2-yl, indol-6-yl, isoquinolin-3-yl, [1,8]-naphthyridine-3-yl, oxazolo[4,5-b]-pyridin-2-yl, quinolin-2-yl, quinolin-3-yl, quinoxalin-2-yl, indan-2-yl and naphthalen-2-yl, 1,3-dioxo-isoindol-2yl, benzimidazol-2-yl, benzothiophen-2-yl, 1H-benzotriazol-5-yl, 1H-indol-5-yl, 3H-benzooxazol-2-one-6-yl, 3H-benzothiazol-2-one-5-yl, 3H-quinazolin-4-one-2-yl, 3H-quinazolin-4-one-6-yl, 4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl, benzo[1,2,3]thiadiazol-6-yl, benzo[1,2,5]thiadiazol-5-yl, benzo[1,4]oxazin-2-one-3-yl, benzothiazol-5-yl, benzothiazol-6-yl, cinnolin-3-yl, imidazo[1,2-a]pyridazin-2-yl, imidazo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyrazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyrimidin-6-yl, pyrazolo[5,1-c][1,2,4]triazin-3-yl, pyrido[1,2-a]pyrimdin-4-one-2-yl, pyrido[1,2-a]pyrimidin-4-one-3-yl, quinazolin-2-yl, quinoxalin-6-yl, thiazolo[3,2-a]pyrimidin-5-one-7-yl, thiazolo[5,4-b]pyridin-2-yl, thieno[3,2-b]pyridin-6-yl, [1,2,3]thiadiazolo[5,4-b]pyridin-6-yl, isoindole-1,3-dione-2-yl,

(a) is non aromatic

(2S)-2,3-dihydro-1H-indol-2-yl, (2S)-2,3-dihydro-benzo[1,4]dioxine-2-yl, 3-(R,S)-3,4-dihydro-2H-benzo[1,4]thiazin-3-yl, 3-(R)-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-3-yl, 3-(S)-(2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-3-yl, 2,3-dihydro-benzo[1,4]dioxan-2-yl,

(b) is non aromatic

1,1,3-trioxo-1,2,3,4-tetrahydro-1 l^6-benzo[1,4] thiazin-6-yl, benzo[1,3]dioxol-5-yl, 4H-benzo[1,4]oxazin-3-one-6-yl, 2,3-dihydro-benzo[1,4]dioxin-6-yl, 2-oxo-2,3-dihydro-benzooxazol-6-yl, 3H-benzooxazol-2-one-6-yl, 3H-benzooxazole-2-thione-6-yl, 3H-benzothiazol-2-one-6-yl, 4H-benzo[1,4]oxazin-3-one-6-yl (3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl), 4H-benzo[1,4]thiazin-3-one-6-yl (3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-yl), 4H-benzo[1,4]oxazin-3-one-7-yl, 4-Oxo-2,3,4,5-tetrahydro-benzo[b][1,4]thiazepine-7-yl, 5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidin-6-yl, benzo[1,3]dioxol-5-yl, 2-oxo-2,3-dihydro-1H-pyrido[2,3-b]thiazin-7-yl, 2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-6-yl, 2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl, 2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-7-yl, 3,4-dihydro-2H-benzo[1,4]oxazin-6-yl, 3,4-dihydro-2H-benzo[1,4]thiazin-6-yl, 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl, 2-oxo-2,3-dihydro-1H-pyrido[3,4-b]thiazin-7-yl, 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-yl, 2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl, 3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-yl, 5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl.

R^{13} is preferably H if in ring (a) or in addition (C_{1-4})alkyl such as methyl or isopropyl when in ring (b). More preferably, in ring (b) R^{13} is H when NR^{13} is bonded to X^3 and (C_{1-4})alkyl when NR^{13} is bonded to X^5.

R^{14} and R^{15} are preferably independently selected from hydrogen, halo, hydroxy, (C_{1-4})alkoxy, trifluoromethoxy, nitro, cyano, aryl(C_{1-4})alkoxy and (C_{1-4})alkylsulphonyl.

More preferably R^{15} is hydrogen and each R^{14} is selected from hydrogen, chloro, fluoro, hydroxy, methoxy, trifluoromethoxy, benzyloxy, nitro, cyano and methylsulphonyl. Most preferably R^{14} is selected from hydrogen, hydroxy, fluorine or nitro. Preferably 0-3 groups R^{14} are substituents other than hydrogen.

More preferred groups R^5 include:
4,6-difluoro-indol-2-yl,
1H-pyrrolo[2,3-b]-pyridin-2-yl,
1H-pyrrolo[3,2-b]-pyridin-2-yl,
8-hydroxy-quinolin-2-yl,
quinoxalin-2-yl,
benzimidazol-2-yl,
benzo[1,2,3]-thiadiazol-5-yl,
4- or 5-fluorobenzimidazol-2-yl,
benzothiophen-2-yl,
4,6-difluoro-1H-benzimidazol-2-yl,
2,2-difluoro-benzo[1,3]dioxol-5-yl,
2,3-Dihydro-benzo[1,4]dioxin-6-yl,
4H-benzo[1,4] oxazin-3-one-6-yl,
4H-benzo[1,4] thiazin-3-one-6-yl,
6-chloro-benzo[1,3]dioxol-5-yl,
7-fluoro-4H-benzo[1,4] oxazin-3-one-6-yl, and
benzo[1,3]dioxol-5-yl.

Most preferred groups R^5 are:
4-fluorobenzimidazol-2-yl,
2,3-Dihydro-benzo[1,4]dioxin-6-yl,
4H-benzo[1,4] thiazin-3-one-6-yl.

When used herein, the term "alkyl" includes groups having straight and branched chains, for instance, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, pentyl and hexyl. The term 'alkenyl' should be interpreted accordingly.

Halo or halogen includes fluoro, chloro, bromo and iodo.

Haloalkyl moieties include 1-3 halogen atoms.

Unless otherwise defined, the term 'heterocyclic' as used herein includes aromatic and non-aromatic, single and fused, rings suitably containing up to four hetero-atoms in each ring selected from oxygen, nitrogen and sulphur, which rings may be unsubstituted or C-substituted by, for example, up to three groups selected from (C_{1-4})alkylthio; halo; carboxy(C_{1-4})alkyl; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl; (C_{1-4})alkoxycarbonyl; formyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; (C_{1-4})alkylcarbonyloxy; (C_{1-4})alkoxycarbonyl(C_{1-4})alkyl; hydroxy; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl; optionally substituted aryl, aryl(C_{1-4})alkyl or aryl(C_{1-4})alkoxy and oxo groups. Each heterocyclic ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring. Compounds within the invention containing a heterocyclyl group may occur in two or more tautometric forms depending on the nature of the heterocyclyl group; all such tautomeric forms are included within the scope of the invention.

Where an amino group forms part of a single or fused non-aromatic heterocyclic ring as defined above suitable optional substituents in such substituted amino groups include H; trifluoromethyl; (C_{1-4})alkyl optionally substituted by hydroxy, (C_{1-6})alkoxy, (C_{1-6})alkylthio, halo or trifluoromethyl; (C_{2-4})alkenyl; aryl; aryl (C_{1-4})alkyl; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; formyl; (C_{1-6})alkylsulphonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl, (C_{2-4})alkenylcarbonyl, (C_{1-4})alkyl or (C_{2-4})alkenyl and optionally further substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl..

When used herein the term 'aryl', includes phenyl and naphthyl, each optionally substituted with up to five, preferably up to three, groups selected from(C_{1-4})alkylthio; halo; carboxy(C_{1-4})alkyl; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl; (C_{1-4})alkoxycarbonyl; formyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; (C_{1-4})alkylcarbonyloxy; (C_{1-4})alkoxycarbonyl(C_{1-4})alkyl; hydroxy; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; nitro; cyano, carboxy; amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl; phenyl, phenyl(C_{1-4})alkyl or phenyl(C_{1-4})alkoxy.

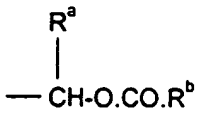
The term 'acyl' includes (C_{1-6})alkoxycarbonyl, formyl or (C_{1-6}) alkylcarbonyl groups.

Some of the compounds of this invention may be crystallised or recrystallised from solvents such as organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

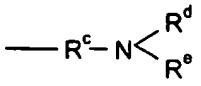
Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 59% of a compound of the formula (I) or pharmaceutically acceptable derivative thereof.

Pharmaceutically acceptable derivatives of the above-mentioned compounds of formula (I) include the free base form or their acid addition or quaternary ammonium salts, for example their salts with mineral acids e.g. hydrochloric, hydrobromic, sulphuric nitric or phosphoric acids, or organic acids, e.g. acetic, fumaric, succinic, maleic, citric, benzoic, p-toluenesulphonic, methanesulphonic, naphthalenesulphonic acid or tartaric acids. Compounds of formula (I) may also be prepared as the N-oxide. Compounds of formula (I) having a free carboxy group may also be prepared as an *in vivo* hydrolysable ester. The invention extends to all such derivatives.

Examples of suitable pharmaceutically acceptable *in vivo* hydrolysable ester-forming groups include those forming esters which break down readily in the human body to leave the parent acid or its salt. Suitable groups of this type include those of part formulae (i), (ii), (iii), (iv) and (v):



(i)



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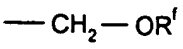

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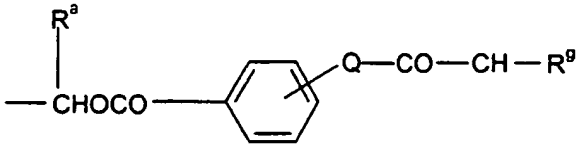
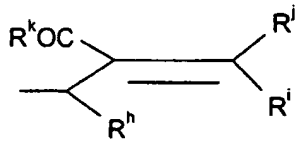


(iv)



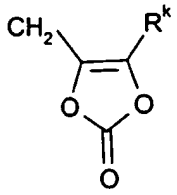
(v)

wherein R^a is hydrogen, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, methyl, or phenyl, R^b is (C_{1-6}) alkyl, (C_{1-6}) alkoxy, phenyl, benzyl, (C_{3-7}) cycloalkyl, (C_{3-7}) cycloalkyloxy, (C_{1-6}) alkyl (C_{3-7}) cycloalkyl, 1-amino (C_{1-6}) alkyl, or 1-$(C_{1-6}$ alkyl)amino (C_{1-6}) alkyl; or R^a and R^b together form a 1,2-phenylene group optionally substituted by one or two methoxy groups; R^c represents (C_{1-6}) alkylene optionally substituted with a methyl or ethyl group and R^d and R^e independently represent (C_{1-6}) alkyl; R^f represents (C_{1-6}) alkyl; R^g represents hydrogen or phenyl optionally substituted by up to three groups selected from halogen, (C_{1-6}) alkyl, or (C_{1-6}) alkoxy; Q is oxygen or NH; R^h is hydrogen or (C_{1-6}) alkyl; R^i is hydrogen, (C_{1-6}) alkyl optionally substituted by halogen, (C_{2-6}) alkenyl, (C_{1-6}) alkoxycarbonyl, aryl or heteroaryl; or R^h and R^i together form (C_{1-6}) alkylene; R^j represents hydrogen, (C_{1-6}) alkyl or (C_{1-6}) alkoxycarbonyl; and R^k represents (C_{1-8}) alkyl, (C_{1-8}) alkoxy, (C_{1-6}) alkoxy(C_{1-6})alkoxy or aryl.

Examples of suitable *in vivo* hydrolysable ester groups include, for example, acyloxy(C_{1-6})alkyl groups such as acetoxymethyl, pivaloyloxymethyl, α-acetoxyethyl, α-pivaloyloxyethyl, 1-(cyclohexylcarbonyloxy)prop-1-yl, and (1-aminoethyl)carbonyloxymethyl; (C_{1-6})alkoxycarbonyloxy(C_{1-6})alkyl groups, such as ethoxycarbonyloxymethyl, α-ethoxycarbonyloxyethyl and propoxycarbonyloxyethyl; di(C_{1-6})alkylamino(C_{1-6})alkyl especially di(C_{1-4})alkylamino(C_{1-4})alkyl groups such as

dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl or diethylaminoethyl; 2-((C_{1-6})alkoxycarbonyl)-2-(C_{2-6})alkenyl groups such as 2-(isobutoxycarbonyl)pent-2-enyl and 2-(ethoxycarbonyl)but-2-enyl; lactone groups such as phthalidyl and dimethoxyphthalidyl.

A further suitable pharmaceutically acceptable *in vivo* hydrolysable ester-forming group is that of the formula:

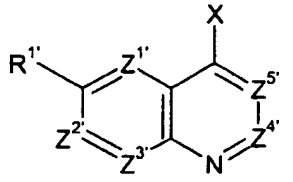


wherein R^k is hydrogen, C_{1-6} alkyl or phenyl.

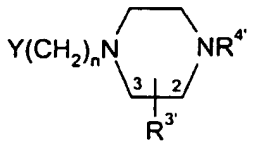
R is preferably hydrogen.

Certain of the above-mentioned compounds of formula (I) may exist in the form of optical isomers, e.g. diastereoisomers and mixtures of isomers in all ratios, e.g. racemic mixtures. The invention includes all such forms, in particular the pure isomeric forms. For examples the invention includes compound in which an A-B group CH(OH)-CH_2 is in either isomeric configuration the *R*-isomer is preferred. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses..

In a further aspect of the invention there is provided a process for preparing compounds of formula (I), or a pharmaceutically acceptable derivative thereof, which process comprises reacting a compound of formula (IV) with a compound of formula (V):



(IV)



(V)

wherein n is as defined in formula (I); $Z^{1'}$, $Z^{2'}$, $Z^{3'}$, $Z^{4'}$, $Z^{5'}$, $R^{1'}$, $R^{3'}$ and $R^{4'}$ are Z^1, Z^2, Z^3, Z^4, Z^5, R^1, R^3 and R^4 as defined in formula (I) or groups convertible thereto; and X and Y may be the following combinations:

(i) X is A'-COW, Y is H and n is 0;

(ii) X is $CR^6{=}CR^8R^9$, Y is H and n is 0;

(iii) X is oxirane, Y is H and n is 0;

(iv) X is N=C=O and Y is H and n is 0;

(v) one of X and Y is CO_2R^y and the other is $CH_2CO_2R^x$;

(vi) X is CHR^6R^7 and Y is $C(=O)R^8$;

(vii) X is $CR^7=PR^z_3$ and Y is $C(=O)R^9$ and n=1;

(viii) X is $C(=O)R^7$ and Y is $CR^9=PR^z_3$ and n=1;

(ix) Y is COW and X is $NHR^{11'}$, NCO or NR11'COW and n=0 or 1 or when n=1 X is COW and Y is $NHR^{11'}$, NCO or NR11'COW;

(x) X is $NHR^{11'}$ and Y is $C(=O)R^8$ and n=1;

(xi) X is $NHR^{11'}$ and Y is CR^8R^9W and n=1;

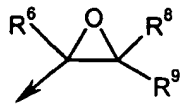
(xii) X is $NR^{11'}COCH_2W$ or $NR^{11'}SO_2CH_2W$ and Y is H and n=0;

(xiii) X is $CR^6R^7SO_2W$ and Y is H and n=0;

(xiv) X is W or OH and Y is CH_2OH and n is 1;

(xv) X is $NHR^{11'}$ and Y is SO_2W or X is $NR^{11'}SO_2W$ and Y is H, and n is 0;

in which W is a leaving group, e.g. halo or imidazolyl; R^x and R^y are (C_{1-6})alkyl; R^z is aryl or (C_{1-6})alkyl; A' and $NR^{11'}$ are A and NR^{11} as defined in formula (I), or groups convertible thereto; and oxirane is:



wherein R^6, R^8 and R^9 are as defined in formula (I);

and thereafter optionally or as necessary converting A', $Z^{1'}$, $Z^{2'}$, $Z^{3'}$, $Z^{4'}$, $Z^{5'}$, $R^{1'}$, $R^{3'}$, $R^{4'}$ and $NR^{11'}$;to A, Z^1, Z^2, Z^3, Z^4, Z^5, R^1, R^3, R^4 and $NR^{11'}$; converting A-B to other A-B, interconverting R^1, R^3 and/or R^4, and/or forming a pharmaceutically acceptable derivative thereof.

Process variant (i) initially produces compounds of formula (I) wherein A-B is A'-CO.

Process variant (ii) initially produces compounds of formula (I) wherein A-B is CHR^6-CR^8R^9.

Process variant (iii) initially produces compounds of formula (I) wherein A-B is $CR^6(OH)$-CR^8R^9.

Process variant (iv) initially produces compounds of formula (I) where A-B is NH-CO.

Process variant (v) initially produces compounds of formula (I) wherein A-B is CO-CH_2 or CH_2-CO.

Process variant (vi) initially produces compounds of formula (I) wherein A-B is CR^6R^7-CR^8OH.

Process variant (vii) and (viii) initially produce compounds of formula (I) wherein A-B is $CR^7=CR^9$.

Process variant (ix) initially produces compounds of formula (I) where A-B is $CO\text{-}NR^{11}$ or $NR^{11}\text{-}CO$.

Process variant (x) initially produces compounds of formula (I) wherein A-B is $NR^{11}\text{-}CHR^8$.

Process variant (xi) initially produces compounds of formula (I) wherein A-B is $NR^{11'}\text{-}CR^8R^9$.

Process variant (xii) initially produces compounds of formula (I) where A-B is $NR^{11'}\text{-}CO$ or $NR^{11'}\text{-}SO_2$ and n=1.

Process variant (xiii) initially produces compounds of formula (I) where A-B is $CR^6R^7\text{-}SO_2$.

Process variant (xiv) initially produces compounds of formula (I) wherein A-B is $O\text{-}CH_2$.

Process variant (xv) initially produces compounds where AB is $NR^{11}SO_2$.

In process variants (i) and (ix) the reaction is a standard amide or urea formation reaction involving e.g.:

1. Activation of a carboxylic acid (e.g. to an acid chloride, mixed anhydride, active ester, O-acyl-isourea or other species), and treatment with an amine (Ogliaruso, M.A.; Wolfe, J.F. in *The Chemistry of Functional Groups (Ed. Patai, S.) Suppl. B: The Chemistry of Acid Derivatives, Pt. 1* (John Wiley and Sons, 1979), pp 442-8; Beckwith, A.L.J. in *The Chemistry of Functional Groups (Ed. Patai, S.) Suppl. B: The Chemistry of Amides (Ed. Zabricky, J.)* (John Wiley and Sons, 1970), p 73 ff. The acid and amine are preferably reacted in the presence of an activating agent such as 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) or 1-hydroxybenzotriazole (HOBT); or

2. The specific methods of:

a. *in situ* conversion of an acid into the amine component by a modified Curtius reaction procedure (Shioiri, T., Murata, M., Hamada, Y., *Chem. Pharm. Bull.* 1987, 35, 2698)

b. *in situ* conversion of the acid component into the acid chloride under neutral conditions (Villeneuve, G. B.; Chan, T. H., *Tetrahedron. Lett.* 1997, 38, 6489).

A' may be, for example. protected hydroxymethylene.

The process variant (ii) is a standard addition reaction using methods well known to those skilled in the art. The process is preferably carried out in a polar organic solvent e.g. acetonitrile in the presence of an organic base e.g. triethylamine.

In process variant (iii) the coupling may be effected in acetonitrile at room temperature in the presence of one equivalent of lithium perchlorate as catalyst (general method of J.E. Chateauneuf *et al, J. Org. Chem.*, 56, 5939-5942, 1991) or more

preferably with ytterbium triflate in dichloromethane. In some cases an elevated temperature such as 40 – 70 °C may be beneficial. Alternatively, the piperazine may be treated with a base, such as one equivalent of butyl lithium, and the resulting salt reacted with the oxirane in an inert solvent such as tetrahydrofuran, preferably at an elevated temperature such as 80°C. Use of a chiral epoxide will afford single diastereomers. Alternatively, mixtures of diastereomers may be separated by preparative HPLC or by conventional resolution through crystallisation of salts formed from chiral acids.

The process variant (iv) is a standard urea formation reaction from the reaction of an isocyanate with an amine and is conducted by methods well known to those skilled in the art (for example see March, J; *Advanced Organic Chemistry, Edition 3* (John Wiley and Sons, 1985), p802-3). The process is preferably carried out in a polar solvent such as N,N-dimethylformamide.

In process variant (v) the process is two step: firstly a condensation using a base, preferably sodium hydride or alkoxide, sodamide, alkyl lithium or lithium dialkylamide, preferably in an aprotic solvent e.g. ether, THF or benzene; secondly, hydrolysis using an inorganic acid, preferably HCl in aqueous organic solvent at 0-100°C. Analogous routes are described in DE330945, EP31753, EP53964 and H. Sargent, J. Am. Chem. Soc. **68**, 2688-2692 (1946). Similar Claisen methodology is described in Soszko et. al., Pr.Kom.Mat. Przyr.Poznan.Tow.Przyj.Nauk., (1962), 10, 15.

In process variant (vi) the reaction is carried out in the presence of a base, preferably organometallic or metal hydride e.g. NaH, lithium diisopropylamide or NaOEt, preferably in an aprotic solvent, preferably THF, ether or benzene at -78 to 25°C (analogous process in Gutswiller et al. (1978) J. Am. Chem. Soc. 100, 576).

In process variants (vii) and (viii) if a base is used it is preferably NaH, KH, an alkyl lithium e.g. BuLi, a metal alkoxide e.g. NaOEt, sodamide or lithium dialkylamide e.g.di- isopropylamide. An analogous method is described in US 3989691 and M.Gates et. al. (1970) J. Amer.Chem.Soc., 92, 205, as well as Taylor et al. (1972) JACS 94, 6218.

In process variant (x) where X or Y is CHO the reaction is a standard reductive alkylation using, e.g., sodium borohydride or sodium triacetoxyborohydride (Gribble, G. W. in *Encyclopedia of Reagents for Organic Synthesis (Ed. Paquette, L. A.)* (John Wiley and Sons, 1995), p 4649).

The process variant (xi) is a standard alkylation reaction well known to those skilled in the art, for example where an alcohol or amine is treated with an alkyl halide in the presence of a base (for example see March, J; *Advanced Organic Chemistry, Edition 3* (John Wiley and Sons, 1985), p364-366 and p342-343). The process is preferably carried out in a polar solvent such as N,N-dimethylformamide

In process variant (xii) the reaction is an alkylation, examples of which are described in J. Med. chem. (1979) 22(10) 1171-6. The compound of formula (IV) may be prepared from the corresponding compound where X is $NHR^{11'}$ by acylation with an appropriate derivative of the acid WCH_2COOH such as the acid chloride or sulphonation with an appropriate derivative of the sulphonic acid WCH_2SO_3H such as the sulphonyl chloride.

In process variant (xiii) the reaction is a standard sulphonamide formation reaction well known to those skilled in the art. This may be e.g. the reaction of a sulphonyl halide with an amine.

In process variant (xiv) where X is W such as halogen, methanesulphonyloxy or trifluoromethanesulphonyloxy, the hydroxy group in Y is preferably converted to an OM group where M is an alkali metal by treatment of an alcohol with a base. The base is preferably inorganic such as NaH, lithium diisopropylamide or sodium. Where X is OH, the hydroxy group in Y is activated under Mitsunobu conditions (Fletcher et.al. J Chem Soc. (1995), 623). Alternatively the X=O and $Y=CH_2OH$ groups can be reacted directly by activation with dichlorocarbodiimide (DCC) (Chem. Berichte 1962, 95, 2997 or Angewante Chemie 1963 75, 377).

In process variant (xv) the reaction is conducted in the presence of an organic base such as triethylamine or pyridine such as described by Fuhrman et.al., J. Amer. Chem. Soc.; **67**, 1245, 1945. The $X=NR^{11'}SO_2W$ or $Y=SO_2W$ intermediates can be formed from the requisite amine e.g. by reaction with SO_2Cl_2 analogously to the procedure described by the same authors Fuhrman et.al., J. Amer. Chem. Soc.; **67**, 1245, 1945.

Reduction of a carbonyl group A or B to CHOH can be readily accomplished using reducing agents well known to those skilled in the art, e.g. sodium borohydride in aqueous ethanol or lithium aluminium hydride in ethereal solution. This is analogous to methods described in EP53964, US384556 and J. Gutzwiller *et al, J. Amer. Chem. Soc.*, 1978, 100, 576.

The carbonyl group A or B may be reduced to CH_2 by treatment with a reducing agent such as hydrazine in ethylene glycol, at e.g. 130-160°C, in the presence of potassium hydroxide.

Reaction of a carbonyl group A or B with an organometallic reagent yields a group where R^6 or R^8 is OH and R^7 or R^9 is alkyl.

A hydroxy group on A or B may be oxidised to a carbonyl group by oxidants well known to those skilled in the art, for example, manganese dioxide, pyridinium chlorochromate or pyridinium dichromate.

A hydroxyalkyl A-B group CHR^6CR^8OH or $CR^6(OH)CHR^8$ may be dehydrated to give the group $CR^6=CR^8$ by treatment with an acid anhydride such as acetic anhydride.

Methods for conversion of $CR^6=CR^8$ by reduction to CHR^6CHR^8 are well known to those skilled in the art, for example using hydrogenation over palladium on carbon as catalyst. Methods for conversion of $CR^6=CR^8$ to give the A-B group $CR^6(OH)CHR^8$ or CHR^6CR^8OH are well known to those skilled in the art for example by epoxidation and subsequent reduction by metal hydrides, hydration, hydroboration or oxymercuration.

An amide carbonyl group may be reduced to the corresponding amine using a reducing agent such as lithium aluminium hydride.

A hydroxy group in A or B may be converted to azido by activation and displacement e.g. under Mitsunobu conditions using hydrazoic acid or by treatment with diphenylphosphorylazide and base, and the azido group in turn may be reduced to amino by hydrogenation.

Examples of groups $Z^{1'}$, $Z^{2'}$, $Z^{3'}$, $Z^{4'}$, $Z^{5'}$, are $CR^{1a'}$ where $R^{1a'}$ is a group convertible to R^{1a}. $Z^{1'}$, $Z^{2'}$, $Z^{3'}$, $Z^{4'}$ and $Z^{5'}$ are preferably Z^1, Z^2, Z^3, Z^4 and Z^5.

$R^{1a'}$ and $R^{1'}$ are preferably R^{1a} and R^1. $R^{1'}$ is preferably methoxy. $R^{3'}$ is R^3 or more preferably hydrogen, vinyl, alkoxycarbonyl or carboxy. $R^{4'}$ is R^4 or more preferably H or an N-protecting group such as t-butoxycarbonyl, benzyloxycarbonyl or 9-fluorenylmethyloxycarbonyl.

Conversions of $R^{1a'}$, $R^{1'}$, $R^{3'}$ and $R^{4'}$ and interconversions of R^{1a}, R^1, R^3 and R^4 are conventional. In compounds which contain an optionally substituted hydroxy group, suitable conventional hydroxy protecting groups which may be removed without disrupting the remainder of the molecule include acyl and alkylsilyl groups.

For example $R^{1'}$ methoxy is convertible to $R^{1'}$ hydroxy by treatment with lithium and diphenylphosphine (general method described in Ireland et. al. (1973) J.Amer.Chem.Soc.,7829) or HBr. Alkylation of the hydroxy group with a suitable alkyl derivative bearing a leaving group such as halide and a protected amino, piperidyl, amidino or guanidino group or group convertible thereto, yields, after conversion/deprotection, R^1 alkoxy substituted by optionally N-substituted amino, piperidyl, guanidino or amidino.

R^3 alkenyl is convertible to hydroxyalkyl by hydroboration using a suitable reagent such as 9-borabicyclo[3.3.1]nonane, epoxidation and reduction or oxymercuration.

R^3 1,2-dihydroxyalkyl can be prepared from $R^{3'}$ alkenyl using osmium tetroxide or other reagents well known to those skilled in the art (see Advanced Organic Chemistry

(Ed. March, J.) (John Wiley and Sons, 1985), p 732-737 and refs. cited therein) or epoxidation followed by hydrolysis (see Advanced Organic Chemistry *(Ed. March, J.)* (John Wiley and Sons, 1985), p 332,333 and refs. cited therein).

R^3 vinyl can be chain extended by standard homologation e.g by conversion to hydroxyethyl followed by oxidation to the aldehyde which is then subjected to a Wittig reaction.

Opening an epoxide $R^{3'}$ group with cyanide anion yields a $CH(OH)-CH_2CN$ group.

Opening an epoxide-containing $R^{3'}$ group with azide anion yields an azide derivative which can be reduced to the amine. Conversion of the amine to a carbamate is followed by ring closure with base to give the 2-oxo-oxazolidinyl containing R^3 group.

Substituents on R^3 alkyl or alkenyl may be interconverted by conventional methods, for example hydroxy may be derivatised by esterification, acylation or etherification. Hydroxy groups may be converted to halogen, thiol, alkylthio, azido, alkylcarbonyl, amino, aminocarbonyl, oxo, alkylsulphonyl, alkenylsulphonyl or aminosulphonyl by conversion to a leaving group and substitution by the required group, hydrolysis or oxidation as appropriate or reaction with an activated acid, isocyanate or alkoxyisocyanate. Primary and secondary hydroxy groups can be oxidised to an aldehyde or ketone respectively and alkyated with a suitable agent such as an organometallic reagent to give a secondary or tertiary alcohol as appropriate. A carboxylate group may be converted to an hydroxymethyl group by reduction of an ester of this acid with a suitable reducing agent such as lithium aluminium hydride.

Substituted 2-oxo-oxazolidinyl containing R^3 groups may be prepared from the corresponding aldehyde by conventional reaction with a glycine anion equivalent, followed by cyclisation of the resulting amino alcohol (M Grauert et al, Ann Chem (1985) 1817, Rozenberg et al, Angew Chem Int Ed Engl (1994) 33(1) 91). The resulting 2-oxo-oxazolidinyl group contains a carboxy group which can be converted to other R^{10} groups by standard procedures.

Carboxy groups within R^3 may be prepared by Jones' oxidation of the corresponding alcohols CH_2OH using chromium acid and sulphuric acid in water/methanol (E.R.H. Jones et al, J.C.S. 1946,39). Other oxidising agents may be used for this transformation such as sodium periodate catalysed by ruthenium trichloride (G.F.Tutwiler *et al*, J.Med.Chem., 1987, *30*(6), 1094), chromium trioxide-pyridine (G. Just *et al*, Synth. Commun. 1979, *9*(7), 613), potassium permanganate (D.E.Reedich *et al*, J. Org. Chem.,1985,*50*(19),3535, and pyridinium chlorochromate (D. Askin *et al*, Tetrahedron Letters, 1988, 29(3), 277.

The carboxy group may alternatively be formed in a two stage process, with an initial oxidation of the alcohol to the corresponding aldehyde using for instance dimethyl sulphoxide activated with oxalyl chloride (N.Cohen *et al*, J. Am. Chem. Soc., 1983, 105, 3661) or dicyclohexylcarbodiimide (R.M.Wengler, Angew. Chim. Int. Ed. Eng., 1985, 24(2), 77), or oxidation with tetrapropylammonium perruthenate (Ley *et al*, J. Chem.Soc. Chem Commun.,1987, 1625). The aldehyde may then be separately oxidised to the corresponding acid using oxidising agents such as silver (II) oxide (R.Grigg *et al*, J. Chem. Soc. Perkin1,1983, 1929), potassium permanganate (A.Zurcher, Helv. Chim. Acta., 1987, 70 (7), 1937), sodium periodate catalysed by ruthenium trichloride (T.Sakata *et al*, Bull. Chem. Soc. Jpn., 1988, 61(6), 2025), pyridinium chlorochromate (R.S.Reddy *et al*, Synth. Commun., 1988, 18(51), 545) or chromium trioxide (R.M.Coates *et al*, J. Am. Chem. Soc.,1982, 104, 2198).

An R^3 CO_2H group may also be prepared from oxidative cleavage of the corresponding diol, $CH(OH)CH_2OH$, using sodium periodate catalysed by ruthenium trichloride with an acetontrile-carbontetrachloride-water solvent system (V.S.Martin *et al,* Tetrahedron Letters, 1988, *29*(22), 2701).

R^3 groups containing a cyano or carboxy group may also be prepared by conversion of an alcohol to a suitable leaving group such as the corresponding tosylate by reaction with para-toluenesulphonyl chloride (M.R.Bell, J. Med. Chem.,1970, 13, 389), or the iodide using triphenylphosphine, iodine, and imidazole (G. Lange, Synth. Commun., 1990, 20, 1473). The second stage is the displacement of the leaving group with cyanide anion (LA.Paquette et al, J. Org. Chem.,1979, 44 (25), 4603; P.A.Grieco et al, J. Org. Chem.,1988, 53 (16), 3658). Finally acidic hydrolysis of the nitrile group gives the desired acids (H.Rosemeyer et al, Heterocycles, 1985, 23 (10), 2669). The hydrolysis may also be carried out with base e.g. potassium hydroxide (H.Rapoport, J. Org. Chem.,1958, 23, 248) or enzymatically (T. Beard et al, Tetrahedron Asymmetry, 1993, 4 (6), 1085).

Other functional groups in R^3 may be obtained by conventional conversions of carboxy or cyano groups.

Tetrazoles are conveniently prepared by reaction of sodium azide with the cyano group (e.g. F. Thomas et al, Bioorg. Med. Chem. Lett., 1996, *6* (6), 631; K.Kubo et al, J. Med. Chem., 1993, 36,2182) or by reaction of azidotri-n-butyl stannane with the cyano group followed by acidic hydrolysis (P.L.Ornstein, J. Org. Chem., 1994, *59*, 7682 and J. Med. Chem, 1996, *39* (11), 2219).

The 3-hydroxy-3-cyclobutene-1,2-dion-4-yl group (e.g. R.M.Soll, Bioorg. Med. Chem. Lett., 1993, *3* (4), 757 and W. A. Kinney, J. Med. Chem., 1992, 35 (25), 4720) can be prepared by the following sequence:- (1) a compound where R3 is $(CH_2)_nCHO$ (n =

0,1,2) is treated with triethylamine, carbon tetrabromide triphenylphosphine to give initially $(CH_2)_nCH=CBr_2$; (2) dehydrobromination of this intermediate to give the corresponding bromoethyne derivative $(CH_2)_nC\equiv CBr$ (for this 2 stage sequence see D. Grandjean et al, Tetrahedron Letters, 1994, *35* (21), 3529); (3) palladium-catalysed coupling of the bromoethyne with 4-(1-methylethoxy)-3-(tri-n-butylstannyl)cyclobut-3-ene-1,2-dione (Liebeskind et al, J. Org. Chem., 1990, *55*, 5359); (4) reduction of the ethyne moity to -CH2CH2- under standard conditions of hydrogen and palladium on charcol catalysis(see Howard et al, Tetrahedron, 1980, *36*, 171); and finally (4) acidic hydrolysis of the methylethoxyester to generate the corresponding 3-hydroxy-3-cyclobutene-1,2-dione group R.M.Soll, Bioorg. Med. Chem. Lett., 1993, *3* (4), 757).

The tetrazol-5-ylaminocarbonyl group may be prepared from the corresponding carboxylic acid and 2-aminotetrazole by dehydration with standard peptide coupling agents such as 1,1'-carbonyldiimidazole (P. L. Ornstein et al, J. Med Chem, 1996, *39* (11), 2232).

The alkyl- and alkenyl-sulphonylcarboxamides are similarly prepared from the corresponding carboxylic acid and the alkyl- or alkenyl-sulphonamide by dehydration with standard peptide coupling agents such as 1,1'-carbonyldiimidazole (P. L. Ornstein et al, J.Med.Chem., 1996, 39 (11), 2232).

The hydroxamic acid groups are prepared from the corresponding acids by standard amide coupling reactions eg N. R. Patel et al, Tetrahedron, 1987, *43* (22), 5375

2,4-thiazolidinedione groups may prepared from the aldehydes by condensation with 2,4-thiazolidinedione and subsequent removal of the olefinic double bond by hydrogenation.

The preparation of 5-oxo-1,2,4-oxadiazoles from nitriles is decribed by Y.Kohara et al, Bioorg. Med. Chem. Lett., 1995, *5*(17), 1903.

1,2,4-triazol-5-yl groups may be prepared from the corresponding nitrile by reaction with an alcohol under acid conditions followed by reaction with hydrazine and then an R^{10}-substituted activated carboxylic acid (see JB Polya in 'Comprehensive Heterocyclic Chemistry' Edition 1 p762, Ed AR Katritzky and CW Rees, Pergamon Press, Oxford 1984 and J.J. Ares et al, J. Heterocyclic Chem., 1991, 28(5), 1197).

NH is converted to NR^4 by conventional means such as amide or sulphonamide formation with an acyl derivative $R^5V'COW$ or $R^5V'SO_2W$, for compounds where U is CO or SO_2 or, where U is CH_2, by reaction with a vinyl derivative R^5-$CH=CH_2$, for example by heating in an alcohol such as ethanol containing an acid such as acetic acid, alkylation with an alkyl halide R^5-V'-CH_2-halide or alkyl derivative R^5-V'-CH_2-W in the presence of base, acylation/reduction or reductive alkylation with an aldehyde R^5-V'-CHO where V' is V or a group convertible thereto such as a dimethyl acetal or 1,3-

dithiane. Such groups are deprotected by conventional means eg dimethyl acetal by hydrolysis using dilute acid in tetrahydrofuran, and 1,3-dithiane using $HgCl_2$ in aqueous acetonitrile (Marshall J. A. et al., J. Org. Chem. 34, 4188 (1969) or $AgNO_2$ and I_2 in tetrahydrofuran (Nishide K. et al., Heterocycles 44(1) 393 (1997).

Where V is a group $CR^{17}R^{18}$ this may be obtained by reduction of a V = CO group followed by derivatisation of the resulting R^{17} = OH group as necessary.

Where one of R^3 and R^6, R^7, R^8 or R^9 contains a carboxy group and the other contains a hydroxy or amino group they may together form a cyclic ester or amide linkage. This linkage may form spontaneously during coupling of the compound of formula (IV) and the piperazine moiety or in the presence of standard peptide coupling agents.

It will be appreciated that under certain circumstances interconvertions may interfere, for example, hydroxy groups in A or B and the piperazine NH will require protection e.g. as a carboxy- or silyl-ester group for hydroxy and as an acyl derivative for piperidine nitrogen, during conversion of $R^{1a'}$, $R^{1'}$, $R^{3'}$ or $R^{4'}$, or during the coupling of the compounds of formulae (IV) and (V).

Compounds of formulae (IV) and (V) are known compounds, (see for example Smith *et al, J. Amer. Chem. Soc.*, 1946, 68, 1301) or prepared analogously, see for example the references cited above for reaction variant (a).

Compounds of formula (IV) where X is $CR^6R^7SO_2W$ may be prepared by a route analogous to that of Ahmed El Hadri *et al, J. Heterocyclic Chem.*, 1993, 30(3), 631. Thus compounds of formula (IV) where X is CH_2SO_2OH may be prepared by reacting the corresponding 4-methyl compound with N-bromosuccinimide, followed by treatment with sodium sulfite. The leaving group W may be converted to another leaving group W, e.g. a halogen group, by conventional methods.

The isocyanate of formula (IV) may be prepared conventionally from a 4-amino derivative such as 4-amino-quinoline, and phosgene, or phosgene equivalent (eg triphosgene) or it may be prepared more conveniently from a 4-carboxylic acid by a "one-pot" Curtius Reaction with diphenyl phosphoryl azide (DPPA) [see T. Shiori et al. *Chem. Pharm. Bull.* **35**, 2698-2704 (1987)].

The 4-amino derivatives are commercially available or may be prepared by conventional procedures from a corresponding 4-chloro derivative by treatment with ammonia (O.G. Backeberg et. al., J. Chem Soc., 381, 1942) or propylamine hydrochloride (R. Radinov et. al., Synthesis, 886, 1986).

4-Alkenyl compounds of formula (IV) may be prepared by conventional procedures from a corresponding 4-halogeno-derivative by e.g. a Heck synthesis as described in e.g. *Organic Reactions*, 1982, 27, 345.

4-Halogeno derivatives of compounds of formula (IV) are commercially available, or may be prepared by methods known to those skilled in the art. A 4-chloroquinoline is prepared from the corresponding quinolin-4-one by reaction with phosphorus oxychloride ($POCl_3$) or phosphorus pentachloride, PCl_5. A 4-chloroquinazoline is prepared from the corresponding quinazolin-4-one by reaction with phosphorus oxychloride ($POCl_3$) or phosphorus pentachloride, PCl_5. A quinazolinone and quinazolines may be prepared by standard routes as described by T.A. Williamson in *Heterocyclic Compounds*, 6, 324 (1957) Ed. R.C. Elderfield.

4-Carboxy derivatives of compounds of formula (IV) are commercially available or may be prepared by conventional procedures for preparation of carboxy heteroaromatics well known to those skilled in the art. For example, quinazolines may be prepared by standard routes as described by T.A. Williamson in *Heterocyclic Compounds*, 6, 324 (1957) Ed. R.C. Elderfield. These 4-carboxy derivatives may be activated by conventional means, e.g. by conversion to an acyl halide or anhydride.

Pyridazines may be prepared by routes analogous to those described in Comprehensive Heterocyclic Chemistry, Volume 3, Ed A.J. Boulton and A. McKillop and napthyridines may be prepared by routes analogous to those described in Comprehensive Heterocyclic Chemistry, Volume 2, Ed A.J. Boulton and A. McKillop.

A 4-oxirane derivative of compounds of formula (IV) is conveniently prepared from the 4-carboxylic acid by first conversion to the acid chloride with oxalyl chloride and then reaction with trimethylsilyldiazomethane to give the diazoketone derivative. Subsequent reaction with 5M hydrochloric acid gives the chloromethylketone. Reduction with sodium borohydride in aqueous methanol gives the chlorohydrin which undergoes ring closure to afford the epoxide on treatment with base, e.g. potassium hydroxide in ethanol-tetrahydrofuran.

Alternatively and preferably, 4-oxirane derivatives can be prepared from bromomethyl ketones which can be obtained from 4-hydroxy compounds by other routes well known to those skilled in he art. For example, hydroxy compounds can be converted to the corresponding 4-trifluoromethanesulphonates by reaction with trifluoromethanesulphonic anhydride under standard conditions (see K. Ritter, Synthesis, 1993, 735). Conversion into the corresponding butyloxyvinyl ethers can be achieved by a Heck reaction with butyl vinyl ether under palladium catalysis according to the procedure of W. Cabri *et al,* J. Org. Chem, 1992, **57** (5), 1481. (Alternatively, the same intermediates can be attained by Stille coupling of the trifluoromethanesulphonates or the analaogous chloro derivatives with (1-ethoxyvinyl)tributyl tin, T. R. Kelly, J. Org. Chem., 1996, **61**, 4623.) The alkyloxyvinyl ethers are then converted into the corresponding bromomethylketones by treatment with N-bromosuccinimide in aqueous

tetrahydrofuran in a similar manner to the procedures of J. F. W. Keana, J. Org. Chem., 1983, **48**, 3621 and T. R. Kelly, J. Org. Chem., 1996, **61**, 4623.

The 4-hydroxyderivatives can be prepared from an aminoaromatic by reaction with methylpropiolate and subsequent cyclisation, analogous to the method described in N. E. Heindel et al, J. Het. Chem., 1969, **6**, 77. For example, 5-amino-2-methoxy pyridine can be converted to 4-hydroxy-6-methoxy-[1,5]naphthyridine using this method.

If a chiral reducing agent such as (+) or (-)-B-chlorodiisopinocampheylborane ['DIP-chloride'] is substituted for sodium borohydride, the prochiral chloromethylketone is converted into the chiral chlorohydrin with ee values generally 85-95% [see C. Bolm *et al, Chem. Ber.* 125, 1169-1190, (1992)]. Recrystallisation of the chiral epoxide gives material in the mother liquor with enhanced optical purity (typically ee 95%).

The (*R*)-epoxide, when reacted with a piperazine derivative gives ethanolamine compounds as single diastereomers with (*R*)-stereochemistry at the benzylic position.

Alternatively, the epoxide may be prepared from the 4-carboxaldehyde by a Wittig approach using trimethylsulfonium iodide [see G.A. Epling and K-Y Lin, *J. Het. Chem.*, 1987, 24, 853-857], or by epoxidation of a 4-vinyl derivative.

4-Hydroxy-1,5-naphthyridines can be prepared from 3-aminopyridine derivatives by reaction with diethyl ethoxymethylene malonate to produce the 4-hydroxy-3-carboxylic acid ester derivative with subsequent hydrolysis to the acid, followed by thermal decarboxylation in quinoline (as for example described for 4-Hydroxy-[1,5]naphthyridine-3-carboxylic acid, J. T. Adams *et al., J.Amer.Chem.Soc.,* 1946, **68**, 1317). A 4-hydroxy-[1,5]naphthyridine can be converted to the 4-chloro derivative by heating in phosphorus oxychloride, or to the 4-methanesulphonyloxy or 4-trifluoromethanesulphonyloxy derivative by reaction with methanesulphonyl chloride or trifluoromethanesulphonic anhydride, respectively, in the presence of an organic base. A 4-amino 1,5-naphthyridine can be obtained from the 4-chloro, 4-methanesulphonyloxy or 4-trifluoromethanesulphonyloxy derivative by reaction with n-propylamine in pyridine.

Similarly, 6-methoxy-1,5-naphthyridine derivatives can be prepared from 3-amino-6-methoxypyridine.

1,5-Naphthyridines may be prepared by other methods well known to those skilled in the art (for examples see P.A. Lowe in "Comprehensive Heterocyclic Chemistry" Volume 2, p581-627, Ed A.R. Katritzky and C.W. Rees, Pergamon Press, Oxford, 1984).

The 4-hydroxy and 4-amino-cinnolines may be prepared following methods well known to those skilled in the art [see A.R. Osborn and K. Schofield, *J. Chem. Soc.* 2100 (1955)]. For example, a 2-aminoacetopheneone is diazotised with sodium nitrite and acid

to produce the 4-hydroxycinnoline with conversion to chloro and amino derivatives as described for 1,5-naphthyridines.

The substituted piperazines of formula (V) are either commercially available or may be synthesised by hydrogenation of the corresponding pyrazines (eg von E. Felder et al. *Helv. Chim. Acta* **33**, 888-896 (1960)], or by diborane reduction of a suitable lactam [eg H.L. Larkins et al. *Tet. Lett.* **27**, 2721-2724 (1986)].

Chiral piperazines may be prepared from chiral 2-(S)- and 2-(R)-piperazinecarboxylic acid. Racemic piperazine-2-carboxylic acid (commercially available) may be resolved by crystallisation of the (S)- and (R)-dicamphor-10-sulfonic acid salts [following the general method of K. Stingl et al. *Tet. Asymmetry* **8**, 979-982 (1997)-described for preparation of 2-(S)-piperazinecarboxylic acid].

Piperazine-2-carboxylic acid may be differentially protected [following the procedure of C.F. Bigge et al. *Tet. Lett.* **30**, 5193-5196 (1989)] by first reacting with 2-(t-butoxycarbonyloxyimino)-2-phenylacetonitrile which selectively reacts on N-4, and then by reacting with benzylchloroformate which reacts on N-1. The 2-carboxylic acid is then methylated (conveniently with TMS-diazomethane). Hydrogenation (over Pd/C) then removes the carbobenzyloxy group, which may be alkylated or acylated with the required R^4 group as described above for the conversion of $R^{4'}$=H to R^4. Reaction with trifluoroacetic acid (optionally in dichloromethane) removes the N-4-butoxycarbonyloxy group to afford the required 4-H piperazine.

The chiral piperazine-2-carboxylic acids may be elaborated to various derivatives, for example, an Arndt-Eistert procedure (involving silver salt mediated rearrangement of a diazoketone) will give chiral 2-acetic acid derivatives (initially via the methyl ester). Reduction of the intermediate ester with standard reducing agents such as lithium aluminium hydride will produce a hydroxymethyl derivative.

Compounds of formula (V) where n=1 may be prepared from the compound where n=0 by homologation eg starting from a compound of formula (V) where Y=CO_2H.

R^5-V'-CH_2-halides, acyl derivatives R^5V'COW and R^5V'SO_2W or aldehydes R^5-V'-CHO, vinyl derivatives R^5-CH=CH_2 and alkyl derivatives R^5-V'-CH_2-W are commercially available or are prepared conventionally. The aldehydes may be prepared by partial reduction of the R^5-V'-ester with lithium aluminium hydride or di-isobutylaluminium hydride or more preferably by reduction to the alcohol, with lithium aluminium hydride or sodium borohydride, followed by oxidation to the aldehyde with manganese (II) dioxide (see *Reductions by the Alumino- and Borohydrides in Organic Synthesis*, 2nd ed., Wiley, N.Y., **1997**; *JOC*, 3197, **1984**; *Org. Synth. Coll.*, 102, **1990**; 136, **1998**; *JOC*, 4260, **1990**; *TL*, 995, **1988**; *JOC*, 1721, **1999**; *Liebigs Ann./Recl.*, 2385,

1997; *JOC*, 5486, 1987). The aldehydes may also be prepared from carboxylic acids in two stages by conversion to a mixed anhydride for example by reaction with isobutyl chloroformate followed by reduction with sodium borohydride (R. J. Alabaster et al., Synthesis, 598, 1989) to give the alcohols and then oxidation with a standard oxidising agent such as pyridinium dichromate or by homologation of the R^5CHO intermediate. Acyl derivatives R^5CH_2COW may be prepared by activation of the R^5-CH_2-ester. R^5-V-CH_2-halides such as bromides may be prepared from the alcohol R^5-V'-CH_2OH by reaction with phosphorus tribromide in DCM/triethylamine. R^5-V'-CH_2-W derivatives such as methanesulphonyl derivatives may be prepared from the alcohol R^5-V'-CH_2OH by reaction with methane sulphonyl chloride. $R^5V'SO_2W$ derivatives may be prepared by a route analogous to that of Ahmed El Hadri *et al, J. Heterocyclic Chem.*, 1993, 30(3), 631. Thus compounds of formula $R^5CH_2SO_2OH$ may be prepared by reacting the corresponding R^5CH_3 compound with N-bromosuccinimide, followed by treatment with sodium sulfite. The leaving group W may be converted to another leaving group W, e.g. a halogen group, by conventional methods. The R^5-V'-U- derivatives may be prepared by various conventional strategies. For example the homologous aldehyde R^5-CHO may be treated with trimethylsulfonium methylsulfate in basic conditions, to give an epoxide intermediate (see *Synth. Commun.*, 749, **1985**) which is then treated with lewis acid, such as trifluoroboron etherate or diethyl etherate, to provide the desired aldehyde (see *JOC*, 1720, **1999**). The aldehyde R^5-CHO could also be treated with an appropriate phosphonium salt, such as (methoxymethyl)triphenylphosphonium chloride, in a Wittig fashion reaction. The resulting enol ether can readily be hydrolysed to homologous aldehydes (*Chem. Ber.*, 2514, **1962**). R^5-COW derivatives can be converted to the aldehyde R^5-V'-CHO in several steps (see *JACS*, 1325, 1986). The R^5COCH_2-halide derivatives may be prepared by standard methods from the R^5CO_2H derivative, for example, by acid chloride formation, conversion to the alpha-diazoketone with diazomethane and reaction with a halogen acid to provide the halomethylketone. Vinyl derivatives R^5-$CH=CH_2$ may be prepared from the corresponding diethylaminoethyl derivative by quaternisation with dimethyl sulphate and heating, resulting in elimination of the charged amino group. The diethylaminoethyl derivative may be prepared from another ethyl derivative eg the hydroxyethyl by conventional amine formation. Alternatively, it may be prepared from a methyl derivative by condensation with diethylamine and formaldehyde.

Where R^5 is an optionally substituted benzoimidazol-2-yl group, the compound of formula (V) where $R^{4'}$ is R^4 may be obtained by reacting N-1 protected piperazine with acrylnitrile, converting the resulting $R^{4'}$ 2-cyanoethyl group with partial hydrolysis to give the 2-ethoxycarbonimidoylethyl group which can then be condensed with an

appropriately substituted 1,2-diaminobenzene to give the required benzoimidazol-2-yl group.

R^5-H heterocycles are commercially available or may be prepared by conventional methods.

Conversions of $R^{1a'}$, $R^{1'}$, $R^{3'}$ and $R^{4'}$ may be carried out on the intermediates of formulae (IV), (V) and (Vb) prior to their reaction to produce compounds of formula (I) in the same way as described above for conversions after their reaction.

The pharmaceutical compositions of the invention include those in a form adapted for oral, topical or parenteral use and may be used for the treatment of bacterial infection in mammals including humans.

The antibiotic compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibiotics.

The composition may be formulated for administration by any route, such as oral, topical or parenteral. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrollidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl

cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to 1.5 to 50 mg/kg per day. Suitably the dosage is from 5 to 20 mg/kg per day.

No toxicological effects are indicated when a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof is administered in the above-mentioned dosage range.

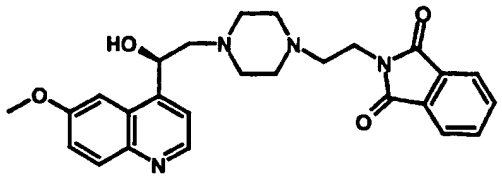
The compound of formula (I) may be the sole therapeutic agent in the compositions of the invention or a combination with other antibiotics or with a β-lactamase inhibitor may be employed.

Compounds of formula (I) are active against a wide range of organisms including both Gram-negative and Gram-positive organisms.

The following examples illustrate the preparation of certain compounds of formula (I) and the activity of certain compounds of formula (I) against various bacterial organisms.

Examples

Example 1 2-(2-{4-[*(R)*-2-Hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperazin-1-yl}-ethyl)-isoindole-1,3-dione dioxalate



(a) 6-Methoxyquinoline-4-carboxylic acid

The title compound was prepared by modification of the procedure described by W.E. Daering and J.D. Chanley, *J. Amer. Chem. Soc.*, 1946, **68**, 586. A mixture of Quinine (225g, 0.70 mol), *tert*-butanol (1 litre) and water (10 ml) was treated with potassium *tert*-butoxide (170g, 1.5 mol). The mixture was stirred at 30°C, while air was bubbled through for 3 days. The mixture was diluted with diethyl ether and water and the layers separated. The aqueous phase was extracted with ethyl acetate. The combined diethyl ether and ethyl acetate extracts were dried over magnesium sulfate and evaporated to give recovered starting material (approximately 100g). The aqueous phase was acidified to pH5 with 5M hydrochloric acid. The precipitate was collected by filtration, washed with water and methanol, then dried to give 6-methoxyquinoline-4-carboxylic acid as a yellow solid (64.6g, 46%).

δH (d-6 DMSO), 6.23-5.95 (1H, m), 5.34-5.06 (2H, m), 3.37-2.92 (5H, m), 2.70 (1H, m), 2.38-2.15 (3H, m), 1.94-1.52 (2H, m).

(b) (*R*)-2-(6-Methoxyquinolin-4-yl)oxirane

A solution of 6-methoxyquinoline-4-carboxylic acid (Example 1(a)) (10g) in dichloromethane was heated under reflux with oxalyl chloride (5ml) and N,N'-dimethylformamide (2 drops) for 1 hour and evaporated to dryness. The residue, in dichloromethane (100ml) was treated with a 2M solution of trimethylsilyldiazomethane in hexane (50ml) and stirred at room temperature for 18 hours. 5M Hydrochloric acid (150ml) was added and the solution was stirred at room temperature for 3 hours. It was basified with sodium carbonate solution, extracted with ethyl acetate and chromatographed on silica gel eluting with ethyl acetate-hexane to give the chloromethyl ketone (4.2g). A batch of the chloromethyl ketone (20g) was reduced with (+)-B-chlorodiisopinocamphenylborane (40g) in dichloromethane (400ml) at room temperature for 18 hours followed by treatment with diethanolamine (30g) for 3 hours. The product was chromatographed on silica gel eluting with ethyl acetate-hexane to give the

chloroalcohol (16.8g), which was dissolved in tetrahydrofuran (100 ml) and reacted with sodium hydroxide (2.6g) in water (13ml) for 1.5 hours. The reaction mixture was evaporated to dryness and chromatographed on silica gel eluting with ethyl acetate/hexane to give the title compound as a solid (10.4 g) (84% ee by chiral HPLC). Recrystallisation from ether-pentane gave mother-liquor (7.0 g) (90% ee).
MS (+ve ion electrospray) m/z 202 (MH+)
The absolute stereochemistry was defined to be *(R)* by an NMR study on the Mosher's esters derived from the product obtained by reaction with 1-*tert*-butylpiperazine.

(c) 4-[*(R)*-2-Hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperazine-1-carboxylic acid *tert*-butyl ester
(R)-2-(6-Methoxyquinolin-4-yl)oxirane (Example 1(b)) (4.30g, 21.37mmol) was dissolved in acetonitrile (30mL). To the solution was added piperazine-1-carboxylic acid *tert*-butyl ester (7.17g, 38.47mmol) and lithium perchlorate (2.27g, 106.4mmol). The resulting slurry was stirred at room temperature for 10 hours and then concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water and the organic phase dried over magnesium sulfate. Concentration *in vacuo* afforded a colourless oil which was subjected to purification by column chromatography on silica gel using a dichloromethane/methanol gradient. This provided the desired compound as a colourless oil (7.65g, 92%).
MS (APCI+) m/z 388 (MH+).

(d) *(R)*-1-(6-Methoxy-quinolin-4-yl)-2-piperazin-1-yl-ethanol
4-[*(R)*-2-Hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperazine-1-carboxylic acid *tert*-butyl ester (Example 1(c)) (3.50g) was dissolved in dichloromethane (10mL) and trifluoroacetic acid (10mL) was added. The resulting solution was stirred at room temperature for 5 hours and then concentrated *in vacuo*. The residue was purified on silica gel, eluting with methanol and dichloromethane. This provided the desired compound which was used without further purification.
MS (APCI+) m/z 288 (MH+).

(e) Title compound
(R)-1-(6-Methoxy-quinolin-4-yl)-2-piperazin-1-yl-ethanol (Example 1(d), crude from above) was dissolved in *N,N'*-dimethylformamide (3mL). To the solution was added potassium carbonate (111mg, 0.807mmol) and 2-(2-bromo-ethyl)-isoindole-1,3-dione (205mg, 0.807mmol). Stirring at room temperature was continued for 3 hours and then the mixture was concentrated *in vacuo*. The residue was purified by column

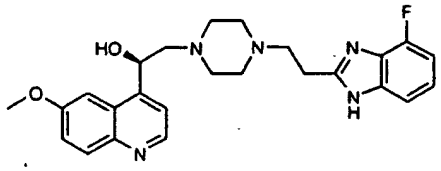
chromatography on silica gel to provide the desired product as a colourless oil (35mg, 11%).

δH (CD_3OD, 250MHz), 8.45-8.43 (1H, d), 7.73-7.67 (2H, m), 7.56-7.09 (6H, m), 5.42-5.38 (1H, dd), 4.25-4.18 (2H, m), 3.74 (3H, s), 3.81-3.58, 2.62-2.41 (12H, m).

MS (APCI+) m/z 461 (MH+).

A solution of the oil (20mg) in dichloromethane (1mL) was added to oxalic acid (8mg) in diethyl ether (10mL) to generate the dioxalate salt. The title compound was isolated by centrifugation, washing with diethyl ether and subsequent drying *in vacuo*.

Example 2 (R)-2-{4-[2-(4-Fluoro-1H-benzoimidazol-2-yl)-ethyl]-piperazin-1-yl}-1-(6-methoxy-quinolin-4-yl)-ethanol



(a) 4-(2-Cyano-ethyl)-piperazine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester

A mixture of 5.17 g (15 mmol) of 9-fluorenylmethyloxylcarbonyl piperazine hydrochloride (RN 215190-22-0), 0.987 ml (15 mmol) of acrylonitrile, 2.081 ml (15 mmol) of triethylamine and 15 ml of isopropylalcohol was stirred 5 min at 40°C followed by 3 h at room temperature. The white precipitate was filtered, washed with diethylether, then dissolved in ethyl acetate. The organic phase was washed with water, dried over magnesium sulphate and concentrated to dryness. The residue was suspended in a small amount of diethyl ether, filtered and dried to afford 3.1 g (yield : 57%) of the title compounds as white crystals.

δH (CDCl3, 200MHz): 7.77(2H, d), 7.57(2H, d), 7.50-7.21(4H, m), 4.45(2H, d), 4.24(1H, t), 3.49(4H, m), 2.74(2H, t), 2.51(2H, t), 2.43(4H, m).

(b) 4-(2-Ethoxycarbonimidoyl-ethyl)-piperazine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester, dihydrochloride

A solution of 1.48 g (4.09 mmol) of 4-(2-cyano-ethyl)-piperazine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester (Example 2(a)) and 239 microliters of ethanol (4.09 mmol) in 5 ml of $CHCl_3$ was saturated, at O°C, by a stream of gaseous hydrochloric acid. The mixture was left overnight in a fridge. The solution was concentrated *in vacuo* and the white residue (1.97 g) used without further purification in the next step.

(c) 4-[2-(4-Fluoro-1H-benzoimidazol-2-yl)-ethyl]-piperazine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester

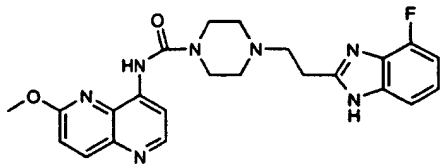
A mixture of 1.97 g (approx. 4 mmol) of crude 4-(2-ethoxycarbonimidoyl-ethyl)-piperazine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester dihydrochloride (Example 2(b)), 0.52 g (4.09 mmol) of 3-fluoro-1,2-diaminobenzene (RN 18645-88-0) and 8 ml of $CHCl_3$ was heated to reflux for 1 h. The mixture was diluted with MDC and neutralised with an aqueous solution of potassium carbonate. The organic phase was washed with water, dried over magnesium sulphate and concentrated. The residue was purified by flash chromatography on silica gel (eluent : first AcOEt, then AcOEt/MeOH : 98/2) to afford 1.15 g (yield 60% over two steps) of the title compound as off-white crystals.
δH (CDCl3, 200MHz): 10.98(1H,br), 7.78(2H, d), 7.59(2H ,d), 7.50-7.22(5H, m), 7.16(1H, m), 6.94(1H, dd), 4.50(2H, d), 4.26(1H, t), 3.58(4H, m), 3.17(2H, t), 2.85(2H, t), 2.55(4H, m).

(d) 4-Fluoro-2-(2-piperazin-1-yl-ethyl)-1H-benzoimidazole
A mixture of 0.49 g (1.04 mmol) of 4-[2-(4-fluoro-1H-benzoimidazol-2-yl)-ethyl]-piperazine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester (Example 2(c)), 156 ul (1.6 mmol) of piperidine and 27 ml of acetonitrile was stirred at room temperature for 21 h. After concentration of the solvent, the residue was purified by flash chromatography over 25 g silica gel (eluent : first CH_2Cl_2/MeOH : 90/10, then 80/20). The most polar fractions were pooled and concentrated affording 0.167 g (yield 65%) of the title compound as a white solid.
δH (CDCl3, 200MHz): 7.30(1H, d), 7.12(1H, m), 6.92(1H, dd), 3.14(2H, t), 3.02(4H, m), 2.82(2H, t), 2.62(4H, m), 1.90(2H, br).

(e) Title compound
A mixture of 160 mg (0.644 mmol) of 4-fluoro-2-(2-piperazin-1-yl-ethyl)-1H-benzoimidazole (Example 2(d)), 118 mg (0.586 mmol) of *(R)*-2-(6-methoxyquinoloin-4-yl)oxirane (Example 1(b)), 62 mg (0.586 mmol) of anhydrous lithium perchlorate and 1.6 ml of anhydrous acetonitrile were stirred for 24 h at room temperature. The solvent was concentrated and the residue dissolved in 15 ml AcOEt. The organic phase was washed with brine, dried over magnesium sulphate and concentrated. The residue was purified by flash chromatography over 25 g silica gel (eluent : CH_2Cl_2/MeOH : 95/5) affording 171 mg (yield 59%) of the title compound as the free base.
A solution of 36 mg (0.396 mmol) of oxalic acid in 2 ml of acetone was added to a solution of 89 mg (0.198 mmol) of the base described above in 2 ml of acetone. The precipitate was filtered, washed with a small amount of diethyl ether and dried to afford 76 mg of the title compound as the oxalate salt as off-white crystals. m.p. = 291-293 °C.

δH (d-6 DMSO, 200MHz): 8.77(1H, d), 7.75(1H, d), 7.62(1H, d), 7.51-7.37(2H, m), 7.32(1H, d), 7.15(1H, m), 6.95(1H, m), 5.71(1H, m), 4.32(5H, br), 3.95(3H, s), 3.35-2.80(14H, m).

Example 3 4-[2-(4-Fluoro-1H-benzoimidazol-2-yl)-ethyl]-piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide



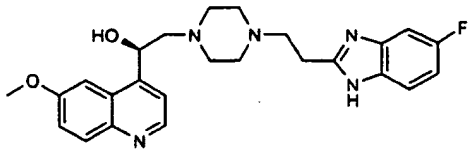
A mixture of 150 mg (0.856 mmol) of 4-amino-6-methoxy-[1,5]naphthyridine (WO00/21948, Example 3(e)), 115 mg (0.942 mmol) of 4-dimethylaminopyridine (DMAP), 194 mg (1.2 mmol) of carbonyl diimidazole and 4 ml of chloroform were stirred for 6 hours. The solvent was concentrated and the residue dissolved in 2 ml of dry DMF. Then, 213 mg (0.856 mmol of 4-fluoro-2-(2-piperazin-1-yl-ethyl)-1H-benzoimidazole (Example 2(d)) were added and the mixture was heated at 70°C for 18 h. The solvent was concentrated *in vacuo* and the residue was dissolved in ethyl acetate and the aqueous phase was washed with water. On standing at room temperature 270 mg of the title compound free base precipitated slowly (yield 70%).

δH (d-6 DMSO, 200MHz): 9.09(1H, s), 8.61(1H, d), 8.21(2H, m), 7.29(2H, d), 7.10(1H, m), 6.93(1H, dd), 4.08(3H, s), 3.58(4H, m), 3.20(1H, br), 3.04(2H, t), 2.85(2H, t), 2.58(4H, m).

The free base described above (100 mg) was salified following the process of example 2(e) to afford 129 mg (yield 92%) of the title compound as the oxalate salt as off-white crystals. m.p. = 263-265°C.

δH (d-6 DMSO, 200MHz): 9.16(1H, s), 8.63(1H, d), 8.32-8.16(2H, m), 7.40-7.24(2H, m), 7.13(1H, m), 6.98(1H, dd), 4.57(5H, br), 4.10(3H, s), 3.73(4H, m), 3.41-3.14(4H, m), 3.03(4H, m).

Example 4 (R)-2-{4-[2-(5-Fluoro-1H-benzoimidazol-2-yl)-ethyl]-piperazin-1-yl}-1-(6-methoxy-quinolin-4-yl)-ethanol



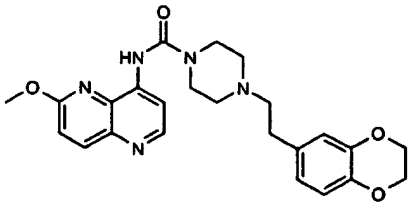
(a) 4-[2-(5-Fluoro-1H-benzoimidazol-2-yl)-ethyl]-piperazine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester

A mixture of 1.15 g (approx. 2.4 mmol) of crude 4-(2-ethoxycarbonimidoyl-ethyl)-piperazine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester dihydrochloride (Example 2(b)), 0.30 g (2.4 mmol) of 4-fluoro-1,2-diaminobenzene (RN 367-31-7) and 4.8 ml of $CHCl_3$ was heated to reflux for 5 h. The mixture was diluted with dichloromethane (MDC) and neutralised with an aqueous solution of potassium carbonate. The organic phase was washed with water, dried over magnesium sulphate and concentrated. The residue was purified by flash chromatography on silica gel (eluent : AcOEt/MeOH : 95/5) to afford 0.49 g (yield 43%) of the title compound as light brown crystals.
δH (CDCl3, 200MHz): 7.77(2H, d), 7.58(2H, d), 7.51-7.18(6H, m), 6.98(1H, td), 5.42(1H, br), 4.51(2H, d), 4.25(1H, t), 3.59(4H, m), 3.17(2H, d), 2.89(2H, t), 2.56(4H, m).

(b) 5-Fluoro-2-(2-piperazin-1-yl-ethyl)-1H-benzoimidazole
Starting with Example 4(a) and following the procedure of Example 2d afforded the desired compound as white crystals.
δH (CDCl3, 200MHz): 7.45(1H, dd), 7.23(1H, dd), 6.96(1H, td), 3.30(2H, br), 3.10(2H, t), 3.02(4H, m), 2.81(2H, t), 2.60(4H, m).

(c) Title compound.
Starting from 100 mg (0.403 mmol) of 5-fluoro-2-(2-piperazin-1-yl-ethyl)-1H-benzoimidazole (Example 4(b)) and following the procedure of example 2(e) afforded 120 mg (yield 0%) of the title compound free base.
δH (CDCl3, 200MHz): 8.78(1H, d), 8.06(1H, d), 7.65(1H, d), 7.53-7.35(2H, m), 7.30-7.17(2H, m), 6.96(1H, td), 5.52(1H, dd), 3.94(3H, s), 3.62(2H, br), 3.17(2H, t), 3.12-2.58(12H, m).
The base described above (120 mg) was salified following the process of example 2(e) to afford 120 mg (yield 71%) of the title compound as the oxalate salt as yellowish crystals.
m.p. 291-293.
δH (d-6 DMSO, 200MHz): 8.76(1H, d), 7.97(1H, d), 7.62(1H, d), 7.58-7.26(4H, m), 7.00(1H, td), 5.70(1H, m), 3.93(3H, s), 3.80(6H, br), 3.33-2.80(14H, m).

Example 5 4-[2-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-ethyl]-piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide, dioxalate.



(a) 6-Oxiranyl-2,3-dihydro-benzo[1,4]dioxine

A mixture of 1,4-benzodioxanecarboxaldehyde [RN 29668-44-8] (1.5 g, 9.14 mmol), trimethylsulfonium methyl sulphate (2.24 g, 11.9 mmol), 35 ml of methylene chloride and 4.6 ml of 50% aqueous sodium hydrochloride were vigorously stirred for 70 hours. The mixture was diluted with 20 ml of water and 40 ml of diethyl ether and the layers separated. The aqueous phase was extracted with diethyl ether. The combined organic phases were washed with 20 ml of water, 20 ml of brine then dried over magnesium sulphate and evaporated to give crude 6-oxiranyl-2,3-dihydro-benzo[1,4]dioxine (1.66 g, quantitative).

δH (CDCl3, 200MHz): 6.88-6.72(3H, m), 4.25(4H, s), 3.76(1H, dd), 3.10(1H, dd), 2.77(1H, dd).

(b) (2,3-Dihydro-benzo[1,4]dioxin-6-yl)-acetaldehyde.

A solution of crude 6-oxiranyl-2,3-dihydro-benzo[1,4]dioxine (Example 5(a), 200 mg, 1.12 mmol) in 20 ml anhydrous diethyl ether was cooled at – 10°C. A 10% solution of boron trifluoride diethyl etherate in diethyl ether (160 ul) was then added and the mixture was stirred for 10 minutes at –10°C. The reaction was quenched at this temperature by addition of 10 ml of a saturated aqueous solution of sodium bicarbonate. The mixture was extracted twice with diethyl ether. The combined organic phases were washed with 10 ml of water, 10 ml of brine then dried over magnesium sulphate and evaporated to give crude (2,3-dihydro-benzo[1,4]dioxin-6-yl)-acetaldehyde (191 mg, 95%) used without further purification in the next step.

δH (CDCl3, 200MHz): 9.70(1H, t), 6.95-6.62(3H, m), 4.26(4H, s), 3.56(2H, d).

(c) 4-(6-Methoxy-[1,5]naphthyridin-4-ylcarbamoyl)-piperazine-1-carboxylic acid tert-butyl ester

A mixture of 4-amino-6-methoxy-[1,5]naphthyridine (1.5 g), 4-dimethylaminopyridine (DMAP) (1.2 g) and carbonyl diimidazole (1.95 g) in chloroform (45 ml) was stirred for 5 hours. The solvent was evaporated and the residue dissolved in dry DMF (20 ml) and piperazine-1-carboxylic acid tert-butyl ester (1.6 g) was added and the solution was heated at 70°C overnight. Water was added and the mixture was extracted with ethyl acetate, dried (magnesium sulfate,) and concentrated to give a solid (1.04 g).

(d) Piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide

The ester (5c) (1.0 g) in dichloromethane (15 ml) and trifluoroacetic acid (8 ml) was stirred at room temperature for 4 hours and evaporated to dryness. Water was added and

excess 15% sodium hydroxide solution and the mixture was extracted with dichloromethane, dried (magnesium sulfate), and evaporated to give a solid (0.4 g)

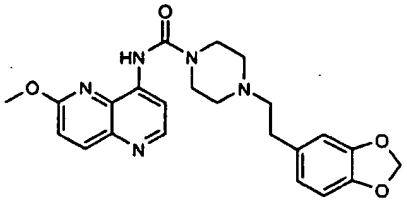
(e) Title compound.

A mixture of (2,3-dihydro-benzo[1,4]dioxin-6-yl)-acetaldehyde (Example 5(b), 138 mg, 0.78 mmol), piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide (Example 5(d) 200 mg, 0.7 mmol), acetic acid (3 drops) and methanol (20 ml) was stirred at room temperature for 0.5 hour, then sodium cyanoborohydride (35 mg, 0.56 mmol) was added and the mixture was stirred at room temperature for 48 hours. The solvent was concentrated and the residue was treated with 0.1 N NaOH (20 ml) then extracted with methylene chloride. The solution was dried over magnesium sulphate and concentrated to dryness. The residue was chromatographed on silica gel eluting with methylene chloride-methanol-ammonia (99-1-0.6) to give the title compound as the free base (184 mg, 41%). δH(d-6 DMSO, 200MHz): 9.10(1H, br), 8.61(1H, d), 8.24(1H, d), 8.21(1H, d), 7.30(1H, d), 6.80-6.60(3H, m), 4.20(4H, s,br), 4.08(3H, s), 3.56(4H, m), 2.63(2H, m), 2.60-2.44(6H,m).

A suspension of the solid obtained above (134 mg, 0.29 mmol) in acetone (15 ml) was treated wit a solution of oxalic acid (74 mg, 0.59 mmol) in acetone (2 ml) to give, after concentration the title compound (208 mg). mp : 158-159°C.

δH(d-6 DMSO, 200MHz): 9.19(1H, br), 8.63(1H,d), 8.26(1H, d), 8.21(1H, d), 7.31(1H,d), 6.87-6.64(3H, m), 5.60(4H, br), 4.21(4H,s,br), 4.10(3H, s), 3.77(4H, m), 3.26-3.00(6H, m), 2.87(2H, m).

Example 6 4-(2-Benzo[1,3]dioxol-5-yl-ethyl)-piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide, dioxalate.



A mixture of benzo[1,3]dioxol-5-yl-acetaldehyde [RN 6543-34-6] (114 mg, 0.7 mmol), piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide (Example 5(d) 200 mg, 0.7 mmol), acetic acid (3 drops) and methanol (20 ml) was stirred at room temperature for a few minutes, then sodium cyanoborohydride (35 mg, 0.6 mmol) was added and the mixture was stirred at room temperature for 2 hours. The solvent was concentrated and the residue was treated with 0.1 N NaOH (20 ml) then extracted twice with methylene chloride (2x20 ml). The organic phase was dried over magnesium sulphate and concentrated to dryness. The residue was chromatographed on silica gel

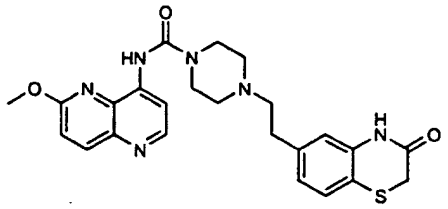
eluting with methylene chloride-methanol-ammonia (99-1-0.6) to give the title compound as the free base (169 mg, 55%).

δH(d-6 DMSO, 200MHz): 9.10(1H, br), 8.61(1H, d), 8.30-8.16(2H, m), 7.7.30(1H, d), 6.88-6.76(2H, m),6.69(1H, dd), 5.96(2H, s), 4.08(3H, s), 3.56(4H, m), 2.69(2H, m), 2.62-2.45(6H, m).

A suspension of the solid obtained above (120 mg, 0.277 mmol) in acetone (15 ml) was treated with a solution of oxalic acid (70 mg, 0.555 mmol) in acetone (2 ml) to give, after concentration, the title compound. mp : 208-210°C.

δH(d-6 DMSO, 200MHz):9.18(1H, br), 8.63(1H, d), 8.26(1H, d), 8.21(1H, d), 7.31(1H, d), 6.92-6.82(2H, m), 6.73(1H, dd), 5.98(2H, s), 4.15(4H, br), 4.10(3H, s), 3.76(4H, m), 3.21-2.97(6H, m), 2.87(2H, m).

Example 7 4-[2-(3-Oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-yl)-ethyl]-piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide.



(a) 2-(4-Fluoro-3-nitro-phenyl)-ethanol.

A solution of (4-fluoro-3-nitro-phenyl)-acetic acid (3 g, 15 mmol) in dimethoxyethane (15 ml) was cooled at – 15°C. 4-Methylmorpholine (1.53 g, 15 mmol) was then added dropwise followed by isobutylchloroformate (2.15 g, 15.7 mmol) also added dropwise. After a few minutes the precipitate of N-methylmorpholine hydrochloride was filtered off and washed three times with dimethoxyethane (3x5 ml). The solution was transferred to a 1 l vial and cooled with an ice-salt bath and treated with a solution of sodium borohydride (0.855 g, 23 mmol) in water (7 ml). A discharge of hydrogen was observed and the solution becoming orange was then diluted with water (375 ml). The solution was extracted three time with ethyl acetate. The organic phase was washed with water, dried over magnesium sulphate and concentrated to dryness. The residue was chromatographed on silica gel eluting with heptane-ethyl acetate (1-1) to give 2-(4-fluoro-3-nitro-phenyl)-ethanol (1.1 g, 39.6%).

δH(CDCl3, 200MHz): 7.95(1H, dd), 7.64-7.46(1H, m), 7.23(1H, dd), 3.92(2H, t), 2.92(2H, t), 1.58(1H, br).

(b) [4-(2-Hydroxy-ethyl)-2-nitro-phenylsulfanyl]-acetic acid.

A mixture of 2-(4-fluoro-3-nitro-phenyl)-ethanol (Example 7(a),1.1 g, 6 mmol), mercaptoacetic acid (0.61 g, 6.6 mmol), potassium carbonate (2.8 g, 20 mmol) and 12 ml

DMF was heated at 70°C for 4 hours. The mixture was poured onto 200 ml of water and the aqueous phase was washed with ethyl acetate. The aqueous phase was then acidified with 1N HCl and extracted three times with 100 ml of methylene chloride. The extracts were dried over magnesium sulphate and evaporated to give [4-(2-hydroxy-ethyl)-2-nitro-phenylsulfanyl]-acetic acid (0.92 g, 60%).
δH (d-6 DMSO, 200MHz): 8.07(1H, d), 7.60(1H, dd), 7.50(1H, d), 3.92(2H, s), 3.63(2H, t), 3.50(2H, br), 2.79(2H, t).

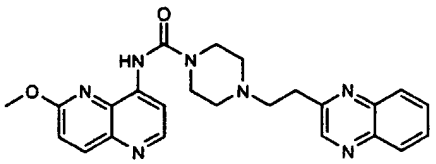
(c) 6-(2-Hydroxy-ethyl)-4H-benzo[1,4]thiazin-3-one.
A mixture of iron powder (1.24 g, 22 mmol), sodium chloride (1.24 g, 21 mmol) and 25 ml of 50% aqueous ethanol was heated under reflux for 15 minutes. A solution of crude [4-(2-hydroxy-ethyl)-2-nitro-phenylsulfanyl]-acetic acid (Example 7(b), 0.92 g, 3.6 mmol) in 5 ml of ethanol was then added quickly and the reaction mixture was heated under reflux for 2 hours. The mixture was filtered on Clarcel® and the filtration cake was rinsed with a small amount of methanol. The alcoholic solution was evaporated to dryness. The residue was dissolved in water and acidified to pH 5 with 1N hydrochloric acid. The precipitate was collected by filtration, washed with water, then dried to give 6-(2-hydroxy-ethyl)-4H-benzo[1,4]thiazin-3-one (0.35 g, 46%).
δH (d-6 DMSO, 200MHz): 10.48(1H, br), 7.20(1H, d), 6.92-6.87(2H, m), 4.65(1H, t), 3.56(2H, q), 3.42(2H, s), 2.64(2H,t).

(d) Methanesulfonic acid 2-(3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-yl)-ethyl ester
A solution of 6-(2-hydroxy-ethyl)-4H-benzo[1,4]thiazin-3-one (Example 7(c), 0.34 g, 1.67 mmol) and 250 ul of triethylamine (0.19 g, 1.8 mmol) in 5 ml of methylene chloride stabilised with amylene was cooled to –15°C by mean of an acetone/ice bath and treated dropwise by 135 ul of methanesulfonyl chloride (1.75 mmol). The ice bath was removed and the mixture stirred 15 hours at room temperature. The organic phase was separated, washed with water, dried over magnesium sulphate and evaporated. The crude product was chromatographed on silica gel eluting with ethyl acetate-heptane (2-1) to give the desired methanesulfonic acid 2-(3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-yl)-ethyl ester (0.36 g, 75%).
δH (d-6 DMSO, 200MHz): 10.55(1H, br), 7.27(1H, d), 6.92(1H, dd), 6.87(1H, d), 4.37(2H, t), 3.45(2H, s), 3.13(3H, s), 2.93(2H, t).

(e) Title compound.
A solution of piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide (Example 5(d) 250 mg, 0.87 mmol), methanesulfonic acid 2-(3-oxo-3,4-dihydro-2H-

benzo[1,4]thiazin-6-yl)-ethyl ester (Example 7(d), 250 mg, 0.87 mmol), triethylamine (135 ul, 0.97 mmol) and acetonitrile (15 ml) was heated under reflux for 18 hours. The mixture was diluted with water. The precipitate was collected by filtration, washed with water then with a small amount of acetonitrile and dried. The crude compound was chromatographed on silica gel eluting with methylene chloride-methanol (96-4) to give the title compound as a white solid (85 mg, 20%). mp : 248-250°C.
δH(d-6 DMSO, 200MHz): 10.51(1H, br), 9.11(1H, br), 8.61(1H, d), 8.30-8.18(2H, m), 7.30-1H, d), 7.21(1H, d), 6.92-6.82(2H, m), 4.08(3H, s), 3.57(4H, m), 3.43(2H,s), 2.69(2H, m), 2.64-2.46(6H, m).

Example 8 4-(2-Quinoxalin-2-yl-ethyl)-piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide.



(a) Diethyl-(2-quinoxalin-2-yl-ethyl)-amine
A solution of diethylamine hydrochloride (3.82 g, 35 mmol) and triethylamine (0.23 ml) in ethanol (1.75 ml) and water (1.75 ml) was added dropwise, at 60°C, to a mixture of 2-methyl-quinoxaline (5 g, 35 mmol), formaldehyde (2.81 g of 37% solution, 35 mmol), triethylamine (0.17 ml) and ethanol (4.6 ml). If necessary the pH was adjusted to 7-7.5 by mean of diluted HCl. Stirring was maintained 16 hours at 60°C. The solvent was concentrated, the residue was diluted with water and extracted with diethyl ether to remove the un-reacted quinoxaline. The aqueous phase was made alkaline with 20% aqueous sodium hydroxide (10 ml) and extracted with ethyl acetate. The organic phase was dried over magnesium sulphate and concentrated. The solid was then chromatographed on silica gel eluting with methylene chloride-methanol (first 95-5 then 90-10 and finally 90-10 plus 0.1% of ammonia) to give diethyl-(2-quinoxalin-2-yl-ethyl)-amine (2.67 g, 37%).
δH(CDCl3, 200MHz): 8.78(1H, s), 8.05(2H, m), 7.72(2H, m), 3.17(2H, m), 3.00(2H, m), 2.64(4H, q), 1.05(6H, t).

(b) 2-Vinyl-quinoxaline.
Dimethyl sulphate (1.07 ml, 11.3 mmol) was added dropwise, while maintaining the mixture temperature below 40°C, to a solution of diethyl-(2-quinoxalin-2-yl-ethyl)-amine (Example 8(a), 2.6g 11.3 mmol) in ethanol (3 ml). The thick mixture was diluted with water (15 ml), triethylamine (1.13 ml) and heated 2 hours on a water bath. After cooling the mixture was extracted with diethyl ether. The organic phase was dried over

magnesium sulphate, concentrated to dryness and the residue was chromatographed on silica gel eluting with heptane-ethyl acetate (3-1) to give) 2-vinyl-quinoxaline (1.16 g, 65.5%).

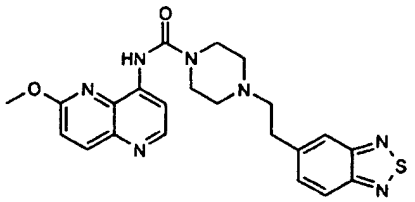
δH(CDCl3, 200MHz): 9.00(1H, s), 8.07(2H, m), 7.75(2H, m), 7.05(1H, dd), 6.48(1H, dd), 5.80(1H, dd).

(c) Title compound.

A mixture of piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide (Example 5(d) 0.403 g, 1.4mmol), 2-vinyl-quinoxaline (Example 8(b), 0.22 g, 1.4 mmol), acetic acid (0.104 ml) and ethanol (5 ml) was heated under reflux for 6 hours. The mixture was then diluted with ethyl acetate and made basic with aqueous sodium hydroxide. The precipitate was collected by filtration and washed with water and a small amount of ethyl acetate. The solid was then dissolved in hot methanol and the insoluble residue, corresponding to an impurity, was discarded. The solution was concentrated to dryness and the residue crystallized in acetonitrile to give the title compound (220 mg, 35%). mp : 138-140°C.

δH(d6-DMSO,200MHz) : 9.08(1H, br), 8.94(1H, s), 8.60(1H, d), 8.32-8.14(2H, m), 8.13-7.97(2H, m), 7.91-7.72(2H, m), 7.29(1H, d), 4.07(3H, s), 3.54(4H, m), 3.21(2H, t), 2.88(2H, t), 2.59(4H, m).

Example 9 4-(2-Benzo[1,2,5]thiadiazol-5-yl-ethyl)-piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide.



(a) Benzo[1,2,5]thiadiazol-5-yl-acetonitrile [RN 89899-11-6].

A mixture of 5-bromomethyl-benzo[1,2,5]thiadiazole [RN 65858-50-6] (7 g, 30 mmol), 50 ml of ethanol and a solution of potassium cyanide (2.3 g, 36 mmol) in 25 ml of water was stirred at 50°C for 15 hours. The alcoholic solution was concentrated and the residue suspended in water. The solid was collected by filtration, washed with water and dried in *vacuo* to give benzo[1,2,5]thiadiazol-5-yl-acetonitrile (2.8 g, 47%)

δH(CDCl3, 200MHz): 8.12-7.97(2H, m), 7.53(1H, dd), 3.96(2H, s).

(b) Benzo[1,2,5]thiadiazol-5-yl-acetic acid [RN 55937-37-6]

A suspension of benzo[1,2,5]thiadiazol-5-yl-acetonitrile (Example 9(a), 2.8 g, 14 mmol) in 6N aqueous hydrochloric acid (70 ml) was heated under reflux for 4 hours. The

mixture was cooled at room temperature and diluted with more water. The precipitate was collected by filtration, washed with water and dried in *vacuo* to give crude benzo[1,2,5]thiadiazol-5-yl-acetic acid (2.8 g, 100%).
δH(DMSO-d6, 200MHz): 12.58(1H, br), 8.03(1H, d), 7.97(1H, d), 7.65(1H, dd), 3.86(2H, s).

(c) 2-Benzo[1,2,5]thiadiazol-5-yl-ethanol.
Borane methylsulfide (1.6 ml) was added dropwise to a cold solution (8-10°C) of crude benzo[1,2,5]thiadiazol-5-yl-acetic acid (Example 9(b), 2.8 g, 14 mmol) in 20 ml of anhydrous THF. Stirring was continued for 1.25 hours while maintaining the temperature below 30°C. The mixture was cooled to 10°C then methanol was added (1.4 ml) and the mixture was left 15 hours in a fridge. The mixture was diluted with ethyl acetate, washed with water then with a saturated aqueous solution of sodium hydrogen carbonate and again with water. The organic phase was separated, dried over magnesium sulphate and evaporated. The residue was triturated in pentane, collected by filtration and dried to give crude) 2-benzo[1,2,5]thiadiazol-5-yl-ethanol (1.8 g, 71%).
δH(CDCl3, 200MHz): 7.94(1H, d), 7.84(1H, d), 7.50(1H, dd), 3.99(2H, t), 3.06(2H, t), 1.58(1H, br).

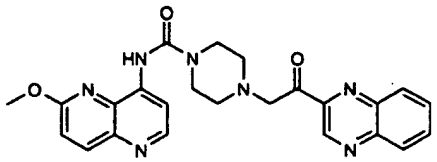
(d) Methanesulfonic acid 2-benzo[1,2,5]thiadiazol-5-yl-ethyl ester.
Methanesulfonyl chloride (450 ul, 5.8 mmol) was added dropwise to an ice cooled solution of 2-benzo[1,2,5]thiadiazol-5-yl-ethanol (Example 9(c), 1 g, 5.5 mmol) and triethylamine (840 ul, 6 mmol) in 20 ml of methylene chloride stabilised over amylene. The reaction mixture was allowed to warm to room temperature and stirred for 16 hours. The organic solution was washed with water, dried over magnesium sulphate and evaporated to dryness. The oily residue was triturated 15 hours with diisopropyl ether. The solid was collected by filtration and dried to give methanesulfonic acid 2-benzo[1,2,5]thiadiazol-5-yl-ethyl ester (1.2 g, 78%) which was used without further purification in the next step.
δH(CDCl3, 200MHz): 7.98(1H, d), 7.87(1H, d), 7.50(1H, dd), 4.54(2H, t), 3.26(2H, t), 2.95(3H, s).

(e) Title compound.
A mixture of piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide (Example 5(d) 0.2 g, 0.7 mmol), methanesulfonic acid 2-benzo[1,2,5]thiadiazol-5-yl-ethyl ester (Example 9(d), 0.2 g, 0.77 mmol), triethylamine (110 ul, 0.77 mmol) and acetonitrile (12 ml) was heated under reflux for 16 hours. The mixture was diluted with

water and extracted 4 times with methylene chloride. The organic phases was dried over magnesium sulphate and concentrated to dryness. The residue was chromatographed on silica gel eluting with methylene chloride-methanol (97-3). The desired fractions were pooled and concentrated. The residue was crystallised by trituration in diethyl ether. The solid was collected by filtration and dried to give the title compound (0.072 g, 23%) as yellow crystals. mp : 188-190°C.

δH(d6-DMSO,200MHz) : 9.10(1H, br), 8.61(1H, d), 8.31-8.16(2H, m), 8.07-7.89(2H, m), 7.68(1H, dd), 7.29(1H,d), 4.08(3H, s), 3.56(4H, m), 3.01(2H, t), 2.71(2H, t), 2.58(4H, m).

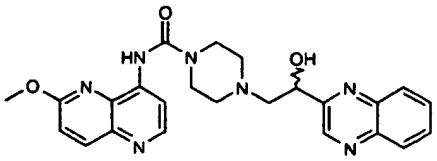
Example 10 4-(2-Oxo-2-quinoxalin-2-yl-ethyl)-piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide.



A mixture of piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide (Example 5(d) 400 mg, 1.39 mmol), 2-bromo-1-quinoxalin-2-yl-ethanone [RN 35970-57-1] (385 mg, 1.53 mmol), diisopropyl-ethylamine (359 mg, 2.78 mmol) and THF (30 ml) was stirred at room temperature for 4 hours. The solvent was concentrated, the residue was dissolved in methylene chloride and the organic phase was washed with water, dried over magnesium sulphate and concentrated to dryness. The residue was chromatographed on silica gel eluting with ethyl acetate-methylene chloride (1-1). The compound was then crystallised by trituration in diethyl ether-ethyl acetate (9-1). The solid was collected by filtration and dried to give the title compound (250 mg, 39%) as yellow crystals. mp : 167-169°C.

δH(d-6 DMSO, 200MHz): 9.38(1H, s), 9.12(1H, br), 8.62(1H, d), 8.32-8.14(4H, m), 8.11-7.91(2H, m), 7.30(1H, d), 4.34(2H, s), 4.01(3H, s), 3.65(4H, m), 2.74(4H, m).

Example 11 4-(2-Hydroxy-2-quinoxalin-2-yl-ethyl)-piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide.

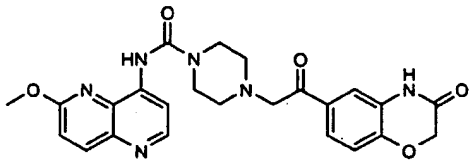


Sodium borohydride (20 mg, 0.526 mmol) was added to a solution of 4-(2-oxo-2-quinoxalin-2-yl-ethyl)-piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide (Example 10, 200 mg, 0.437 mmol) in methanol (5 ml) and the mixture was stirred at room temperature for 2 hours. The mixture was carefully diluted with water and

extracted twice with ethyl acetate (2x50 ml). The organic phase was washed with water, dried over magnesium sulphate and concentrated to dryness to give the title compound (100 mg, 49%). mp : 133-135°C.

δH(CDCl3, 200MHz): 9.12(1H, s), 9.06(1H, br), 8.66(1H, d), 8.31(1H, d), 8.22(1H, d), 8.00-8.20(2H, m), 7.72-7.89(2H, m), 7.15(1H, d), 5.14(1H, dd), 4.34(1H, br), 4.07(3H, s), 3.88-3.58(4H,m), 3.08-2.62(6H, m).

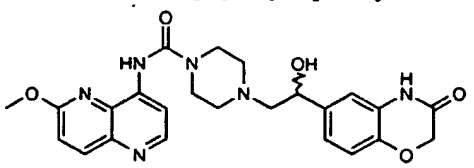
Example 12 4-[2-Oxo-2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-ethyl]-piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide.



A mixture of piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide (Example 5(d) 450 mg, 1.56 mmol), 6-(2-chloro-ethanoyl)-4H-benzo[1,4]oxazin-3-one [26518-76-3] (345 mg, 1.53 mmol), diisopropyl-ethylamine (DIEA) (359 mg, 2.78 mmol) and THF (25 ml) was stirred at room temperature for 16 hours. The reaction being not finished, the solvent was concentrated, the residue was dissolved in acetonitrile, 200 mg of DIEA were added and the mixture was heated under reflux for 5 hours. After cooling the solid formed was collected by filtration, washed 3 times with a small amount of acetonitrile then 2 times with water and dried to give the title compound as off-white crystals (650 mg, 87%). mp : 274-276.

δH(d6-DMSO,200MHz) :10.88(1H, br), 9.08(1H, s), 8.60(1H, d), 8.31-8.12(2H, m), 7.67(1H, dd), 7.57(1H, d), 7.28(1H, d), 7.04(1H, d), 4.69(2H,s), 4.07(3H,s), 3.82(2H, s), 3.58(4H, m), 2.61(4H, m).

Example 13 4-[2-Hydroxy-2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-ethyl]-piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide.

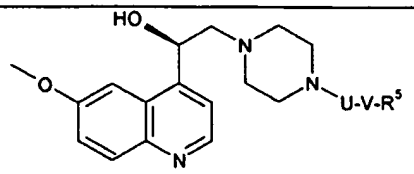


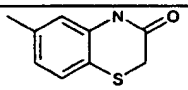
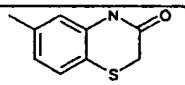
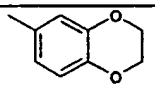
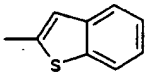
Sodium borohydride (24 mg, 0.63 mmol) was added to a suspension of 4-[2-oxo-2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-ethyl]-piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide (Example 12, 250 mg, 0.52 mmol) in methanol (10 ml) and the mixture was heated to reflux for 3 hours. This process, addition of 25 mg of sodium borohydride followed by 3 hours of reflux was repeated four times. The solid (unreacted starting material) was filtered off and the solution was concentrated to

dryness. The residue was chromatographed on silica gel eluting with ethyl acetate-methanol (first 99-1, then 98-2 finally 97-3) to give the title compound (55 mg, 22%) as white crystals. mp : 231-233°C.

δH(CDCl3, 200MHz) : 9.06(1H, s), 8.66(1H, d), 8.32(1H, d), 8.23(1H, d), 7.90(1H, s), 7.15(1H, d), 7.00-6.82(3H, m), 4.76(1H, dd), 4.61(2H, s), 4.08(3H, s), 3.73(4H, m), 3.00-2.80(2H, m), 2.72-2.48(4H, m), 1.67(1H, br).

The following compounds were prepared by procedures analogous to those described herein:



Example	Salt	-U-V-	R^5
14	B	$-CH_2-CH_2-$	
15	R	$-CH_2-CH(OH)-$	
16	R	$-CH_2-CH(OH)-$	
17	S	$-CO-CH_2-$	

Salts: B = dihydrochloride
R = trihydrochloride
S = mesylate

Biological Activity

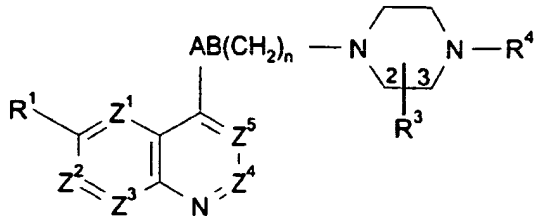
The MIC (μg/ml) of test compounds against various organisms was determined:
S. aureus Oxford, S. aureus WCUH29, S. pneumoniae 1629, S. pneumoniae N1387, S. pneumoniae ERY 2, H. influenzae Q1, E. faecalis 7.

Examples 1-9, 12 and 16 have an MIC of less than or equal to 0.25μg/ml against one or more of the above range of gram positive and gram negative bacteria.

Examples 10, 14 and 15 have an MIC of less than or equal to 2μg/ml against one or more of the above range of gram positive and gram negative bacteria.

Claims

1. A compound of formula (I) or a pharmaceutically acceptable derivative thereof:



(I)

wherein:

one of Z^1, Z^2, Z^3, Z^4 and Z^5 is N, one is CR^{1a} and the remainder are CH, or one of Z^1, Z^2, Z^3, Z^4 and Z^5 is CR^{1a} and the remainder are CH;

R^1 and R^{1a} are independently selected from hydrogen; hydroxy; (C_{1-6}) alkoxy optionally substituted by (C_{1-6})alkoxy, amino, piperidyl, guanidino or amidino any of which is optionally N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{1-6})alkoxy-substituted (C_{1-6})alkyl; halogen; (C_{1-6})alkyl; (C_{1-6})alkylthio; trifluromethyl; nitro; azido; acyl; acyloxy; acylthio; (C_{1-6})alkylsulphonyl; (C_{1-6})alkylsulphoxide; arylsulphonyl; arylsulphoxide or an amino, piperidyl, guanidino or amidino group optionally N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups,
provided that when none of Z^1, Z^2, Z^3, Z^4 and Z^5 is N, then R^1 is not hydrogen;

R^3 is hydrogen; or
R^3 is in the 2- or 3-position and is:
carboxy; (C_{1-6})alkoxycarbonyl; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, trifluoromethylsulphonyl, (C_{2-6})alkenylsulphonyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl or (C_{2-6})alkenyl; cyano; tetrazolyl; 2-oxo-oxazolidinyl optionally substituted by R^{10}; 3-hydroxy-3-cyclobutene-1,2-dione-4-yl; 2,4-thiazolidinedione-5-yl; tetrazol-5-ylaminocarbonyl; 1,2,4-triazol-5-yl optionally substituted by R^{10}; or 5-oxo-1,2,4-oxadiazol-3-yl; or

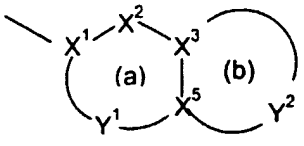
(C_{1-4})alkyl or ethenyl optionally substituted with any of the groups listed above for R^3 and/or 0 to 2 groups R^{12} independently selected from:

halogen; (C_{1-6})alkylthio; trifluoromethyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; (C_{2-6})alkenylcarbonyl; hydroxy optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylcarbonyl or (C_{2-6})alkenylcarbonyl; amino optionally mono- or disubstituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, (C_{2-6})alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl or (C_{2-6})alkenyl; oxo; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or (C_{1-6})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;

in addition when R^3 is disubstituted with a hydroxy or amino containing substituent and a carboxy containing substituent these may optionally together form a cyclic ester or amide linkage, respectively;

R^{10} is selected from (C_{1-4})alkyl; (C_{2-4})alkenyl and aryl any of which may be optionally substituted by a group R^{12} as defined above; carboxy; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, trifluoromethylsulphonyl, (C_{2-6})alkenylsulphonyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl;

R^4 is a group –U-V-R^5 where R^5 is an optionally substituted bicyclic carbocyclic or heterocyclic ring system (A):



(A)

containing up to four heteroatoms in each ring in which

at least one of rings (a) and (b) is aromatic;

X^1 is C or N when part of an aromatic ring or CR^{14} or N when part of a non aromatic ring;

X^2 is N, NR^{13}, O, $S(O)_x$, CO or CR^{14} when part of an aromatic or non-aromatic ring or may in addition be $CR^{14}R^{15}$ when part of a non aromatic ring;

X^3 and X^5 are independently N or C;

Y^1 is a 0 to 4 atom linker group each atom of which is independently selected from N, NR^{13}, O, $S(O)_x$, CO and CR^{14} when part of an aromatic or non-aromatic ring or may additionally be $CR^{14}R^{15}$ when part of a non aromatic ring,

Y^2 is a 2 to 6 atom linker group, each atom of Y^2 being independently selected from N, NR^{13}, O, $S(O)_x$, CO and CR^{14} when part of an aromatic or non-aromatic ring or may additionally be $CR^{14}R^{15}$ when part of a non aromatic ring;

each of R^{14} and R^{15} is independently selected from: H; (C_{1-4})alkylthio; halo; carboxy(C_{1-4})alkyl; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl; (C_{1-4})alkoxycarbonyl; formyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; (C_{1-4})alkylcarbonyloxy; (C_{1-4})alkoxycarbonyl(C_{1-4})alkyl; hydroxy; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl; aryl; aryl(C_{1-4})alkyl; aryl(C_{1-4})alkoxy;

each R^{13} is independently H; trifluoromethyl; (C_{1-4})alkyl optionally substituted by hydroxy, (C_{1-6})alkoxy, (C_{1-6})alkylthio, halo or trifluoromethyl; (C_{2-4})alkenyl; aryl; aryl (C_{1-4})alkyl; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; formyl; (C_{1-6})alkylsulphonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl, (C_{2-4})alkenylcarbonyl, (C_{1-4})alkyl or (C_{2-4})alkenyl and optionally further substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl;

U is selected from CO, SO_2 and CH_2 and V is $CR^{17}R^{18}$ or U is CH_2 and V is CO or SO_2;

R^{17} and R^{18} are independently selected from hydrogen, hydroxy optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylcarbonyl or (C_{2-6})alkenylcarbonyl; and amino optionally mono- or disubstituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, $(C_{2-}$

$_{6}$)alkenylcarbonyl, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, (C_{2-6})alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;

n is 0 and AB is $NR^{11}CO$, $CO\text{-}CR^8R^9$, $CR^6R^7\text{-}CO$, $NHR^{11}SO_2$, $CR^6R^7\text{-}SO_2$ or $CR^6R^7\text{-}CR^8R^9$, provided that R^8 and R^9 are not optionally substituted hydroxy or amino and R^6 and R^8 do not represent a bond:
or n is 1 and AB is $NR^{11}CO$, $CO\text{-}CR^8R^9$, $CR^6R^7\text{-}CO$, $NR^{11}SO_2$, $CONR^{11}$, $CR^6R^7\text{-}CR^8R^9$, $O\text{-}CR^8R^9$ or $NR^{11}\text{-}CR^8R^9$;

and wherein:
each of R^6, R^7, R^8 and R^9 is independently selected from: H; (C_{1-6})alkoxy; (C_{1-6})alkylthio; halo; trifluoromethyl; azido; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; (C_{2-6})alkenylcarbonyl; hydroxy, amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or (C_{1-6})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;
or R^6 and R^8 together represent a bond and R^7 and R^9 are as above defined;

and each R^{11} is independently H; trifluoromethyl; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl or (C_{2-6})alkenyl and optionally further substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;

or where one of R^3 and R^6, R^7, R^8 or R^9 contains a carboxy group and the other contains a hydroxy or amino group they may together form a cyclic ester or amide linkage.

2. A compound according to claim 1 wherein Z^5 is CH or N, Z^3 is CH or CF and Z^1, Z^2 and Z^4 are each CH, or Z^1 is N, Z^3 is CH or CF and Z^2, Z^4 and Z^5 are each CH.

3. A compound according to any preceding claim wherein R^1 is methoxy and R^{1a} is H or when Z^3 is CR^{1a} it may be C-F.

4. A compound according to any preceding claim wherein R^3 is hydrogen; $CONH_2$; 1-hydroxyalkyl; CH_2CO_2H; CH_2CONH_2; -$CONHCH_2CONH_2$; 1,2-dihydroxyalkyl; CH_2CN; 2-oxo-oxazolidin-5-yl and 2-oxo-oxazolidin-5-yl(C_{1-4}alkyl).

5. A compound according to any preceding claim wherein n is 0 and either A is CHOH and B is CH_2 or A is NH and B is CO.

6. A compound according to any preceding claim wherein –U-V- is –$(CH_2)_2$-.

7. A compound according to any preceding claim wherein R^5 is an aromatic heterocyclic ring (A) having 8-11 ring atoms including 2-4 heteroatoms of which at least one is N or NR^{13} or the heterocyclic ring (A) has ring (a) aromatic and ring (b) non-aromatic and Y^2 has 3-5 atoms including NR^{13}, O or S bonded to X^5 and NHCO bonded via N to X^3, or O or NH bonded to X^3.

8. A compound according to claim 1 selected from:
2-(2-{4-[*(R)*-2-Hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-piperazin-1-yl}-ethyl)-isoindole-1,3-dione
(R)-2-{4-[2-(4-Fluoro-1H-benzoimidazol-2-yl)-ethyl]-piperazin-1-yl}-1-(6-methoxy-quinolin-4-yl)-ethanol
4-[2-(4-Fluoro-1H-benzoimidazol-2-yl)-ethyl]-piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
(R)-2-{4-[2-(5-Fluoro-1H-benzoimidazol-2-yl)-ethyl]-piperazin-1-yl}-1-(6-methoxy-quinolin-4-yl)-ethanol 4-[2-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-ethyl]-piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
4-(2-Benzo[1,3]dioxol-5-yl-ethyl)-piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
4-[2-(3-Oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-yl)-ethyl]-piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
4-(2-Quinoxalin-2-yl-ethyl)-piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
4-(2-Benzo[1,2,5]thiadiazol-5-yl-ethyl)-piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
4-(2-Oxo-2-quinoxalin-2-yl-ethyl)-piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
4-(2-Hydroxy-2-quinoxalin-2-yl-ethyl)-piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide

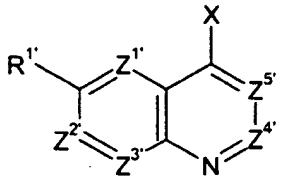
4-[2-Oxo-2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-ethyl]-piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide and
4-[2-Hydroxy-2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-ethyl]-piperazine-1-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
or a pharmaceutically acceptable derivative thereof.

9. A method of treatment of bacterial infections in mammals, particularly in man, which method comprises the administration to a mammal in need of such treatment an effective amount of a compound according to claim 1.

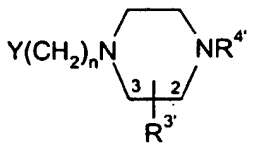
10. The use of a compound according to claim 1, in the manufacture of a medicament for use in the treatment of bacterial infections in mammals.

11. A pharmaceutical composition comprising a compound according to claim 1, and a pharmaceutically acceptable carrier.

12. A process for preparing a compound according to claim 1, which process comprises reacting a compound of formula (IV) with a compound of formula (V):



(IV)



(V)

wherein n is as defined in formula (I); $Z^{1'}$, $Z^{2'}$, $Z^{3'}$, $Z^{4'}$, $Z^{5'}$, $R^{1'}$, $R^{3'}$ and $R^{4'}$ are Z^1, Z^2, Z^3, Z^4, Z^5, R^1, R^3 and R^4 as defined in formula (I) or groups convertible thereto; and X and Y may be the following combinations:

(i) X is A'-COW, Y is H and n is 0;
(ii) X is $CR^6=CR^8R^9$, Y is H and n is 0;
(iii) X is oxirane, Y is H and n is 0;
(iv) X is N=C=O and Y is H and n is 0;
(v) one of X and Y is CO_2R^y and the other is $CH_2CO_2R^x$;
(vi) X is CHR^6R^7 and Y is $C(=O)R^8$;
(vii) X is $CR^7=PR^z{}_3$ and Y is $C(=O)R^9$ and n=1;
(viii) X is $C(=O)R^7$ and Y is $CR^9=PR^z{}_3$ and n=1;

(ix) Y is COW and X is $NHR^{11'}$, NCO or NR11'COW and n=0 or 1 or when n=1 X is COW and Y is $NHR^{11'}$, NCO or NR11'COW;

(x) X is $NHR^{11'}$ and Y is $C(=O)R^8$ and n=1;

(xi) X is $NHR^{11'}$ and Y is CR^8R^9W and n=1;

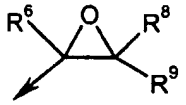
(xii) X is $NR^{11'}COCH_2W$ or $NR^{11'}SO_2CH_2W$ and Y is H and n=0;

(xiii) X is $CR^6R^7SO_2W$ and Y is H and n=0;

(xiv) X is W or OH and Y is CH_2OH and n is 1;

(xv) X is $NHR^{11'}$ and Y is SO_2W or X is $NR^{11'}SO_2W$ and Y is H, and n is 0;

in which W is a leaving group, e.g. halo or imidazolyl; R^x and R^y are (C_{1-6})alkyl; R^z is aryl or (C_{1-6})alkyl; A' and $NR^{11'}$ are A and NR^{11} as defined in formula (I), or groups convertible thereto; and oxirane is:



wherein R^6, R^8 and R^9 are as defined in formula (I);

and thereafter optionally or as necessary converting A', $Z^{1'}$, $Z^{2'}$, $Z^{3'}$, $Z^{4'}$, $Z^{5'}$, $R^{1'}$, $R^{3'}$, $R^{4'}$ and $NR^{11'}$;to A, Z^1, Z^2, Z^3, Z^4, Z^5, R^1, R^3, R^4 and $NR^{11'}$; converting A-B to other A-B, interconverting R^1, R^3 and/or R^4, and/or forming a pharmaceutically acceptable derivative thereof.

INTERNATIONAL SEARCH REPORT

Itional Application No
PCT/GB 01/05653

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/14 C07D471/04 A61K31/495 A61P31/04
//(C07D471/04,221:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BE 645 602 A (RHONE-POULENC S.A.) 23 September 1964 (1964-09-23) examples 14,21	1
Y	page 5, paragraph 5	1-12
Y	WO 99 37635 A (COATES WILLIAM JOHN ;MASTERS PHILIP JOHN (GB); WARRACK JULIE DOROT) 29 July 1999 (1999-07-29) cited in the application Compounds (I) abstract	1-12
Y	WO 00 21948 A (HATTON IAN KEITH ;PEARSON NEIL DAVID (GB); SMITHKLINE BEECHAM PLC) 20 April 2000 (2000-04-20) cited in the application Compounds (I) abstract	1-12

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 April 2002	16/04/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fritz, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 21952 A (DAVIES DAVID THOMAS ;MARKWELL ROGER EDWARD (GB); PEARSON NEIL DAVI) 20 April 2000 (2000-04-20) cited in the application Compounds (I) abstract	1-12

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/05653

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
BE 645602 A	23-09-1964	FR 1427620 A	11-02-1966
		FR 86513 E	25-02-1966
		CH 431525 A	15-03-1967
		DE 1228265 B	
		DK 112526 B	23-12-1968
		FR 2905 M	
		GB 1027963 A	04-05-1966
		NL 6403210 A	28-09-1964
		OA 1394 A	04-07-1969
		SE 302303 B	15-07-1968
		US 3230223 A	18-01-1966
WO 9937635 A	29-07-1999	AU 2717899 A	09-08-1999
		CA 2318842 A1	29-07-1999
		WO 9937635 A1	29-07-1999
		EP 1051413 A1	15-11-2000
		JP 2002501061 T	15-01-2002
		ZA 9900520 A	25-07-2000
WO 0021948 A	20-04-2000	AU 6114699 A	01-05-2000
		EP 1127057 A1	29-08-2001
		WO 0021948 A1	20-04-2000
WO 0021952 A	20-04-2000	AU 6339599 A	01-05-2000
		WO 0021952 A1	20-04-2000
		EP 1121355 A1	08-08-2001